THE American Journal OF Gastroenterology

VOL. 21, NO. 5 MAY, 1954

Nineteenth Annual Convention
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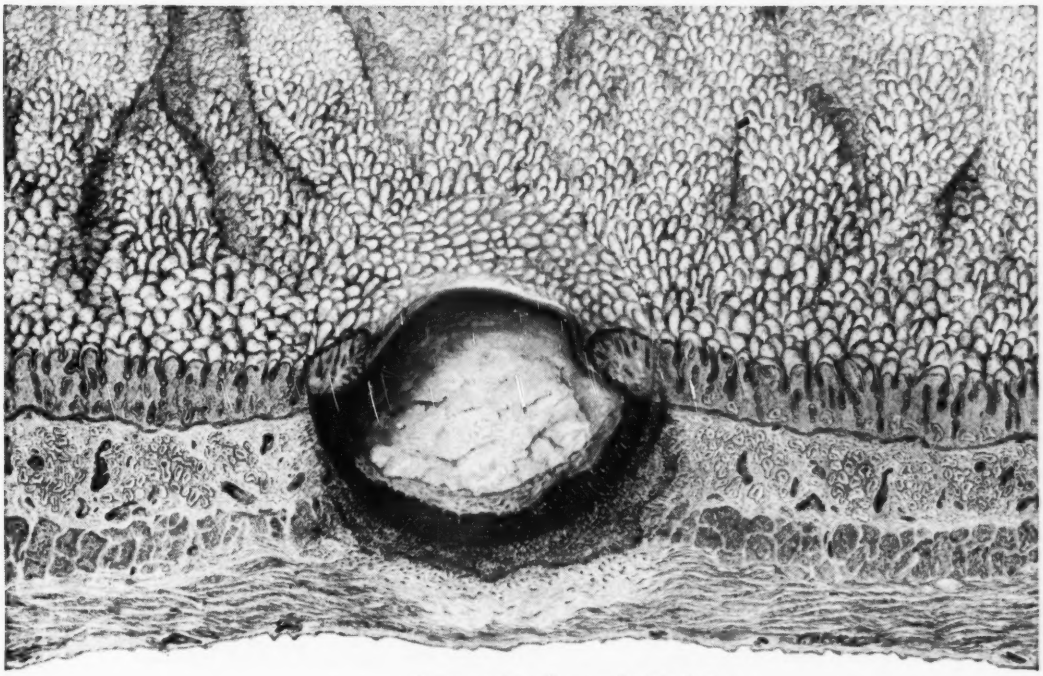

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1. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology *23*:252 (Feb.) 1953.
2. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, Gastroenterology *25*:416 (Nov.) 1953.

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THE American Journal OF Gastroenterology

(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

contents:

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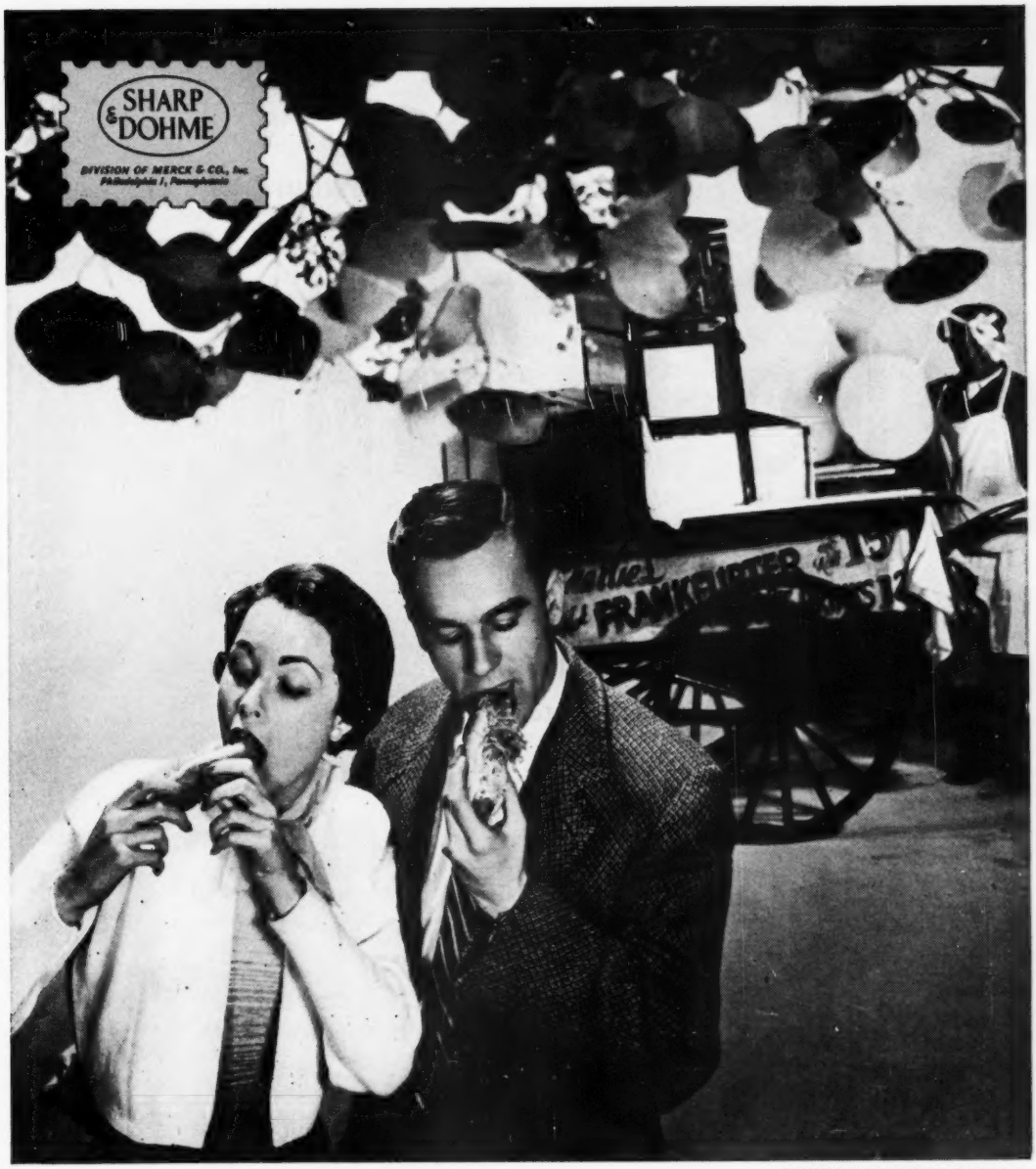

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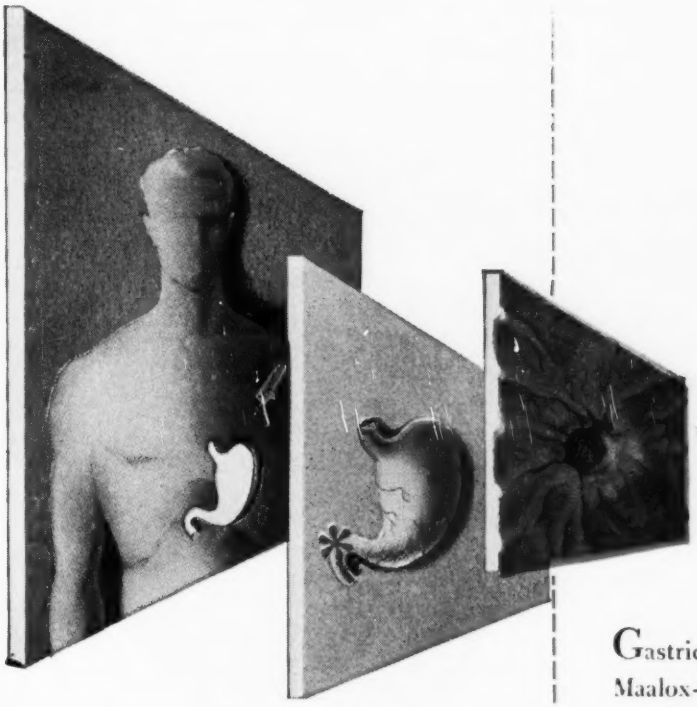

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VOLUME 21 MAY, 1954 NUMBER 5

ACHOLIA*

WHITE BILE IN THE COMMON DUCT WITH RECOVERY

HERBERT R. HAWTHORNE, M.D.‡

and

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Philadelphia, Pa.

Acholia—the absence of bile in the intestinal tract—is usually caused by an obstruction to bile flow in the common bile duct. The obstruction produces an increase in size and capacity of the bile ducts and gallbladder. There is, concurrently, an increase in intracholedochal pressure. When this pressure exceeds 300 mm. (of bile), the hepatic cell may not function[4].

There are several safety factors which maintain hepatic function. Since the bile duct has elastic walls, its contained volume may increase to compensate for the increase in fluid pressure. In addition, fluid constituents of bile can be absorbed. Not only do these mechanisms protect the function of liver cells but they also may delay the clinical recognition of jaundice.

In patients with bile duct obstruction, an inflammatory exudate may surround the bile capillaries to compress the "canal of Hering" or the perilobular ductules may rupture[6,14]. As obstruction continues bile thrombi are found in the hepatic canaliculi; jaundice appears. Irritation phenomena in the liver subsequently appear:

(a) bile pigment is deposited in the hepatic parenchyma,

(b) hepatic cells show local necrosis,

(c) bile canaliculi proliferate,

(d) the hepatic parenchyma is infiltrated by small, round cells,

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†Associate in Surgery, Graduate School of Medicine, University of Pennsylvania.

(e) periductal tissues in the liver undergo hyperplasia and fibrosis.

Despite these organic changes following obstruction to bile flow, hepatic cellular function can continue[9]. Progressive, unrelieved obstruction is fatal, however, by reason of hepatic or hepatorenal insufficiency[7].

In an occasional patient, whether the obstruction to bile flow be calculous, inflammatory or malignant, the liver cells fail to excrete or produce bile. This failure may not be recognized by the clinician or the pathologist.

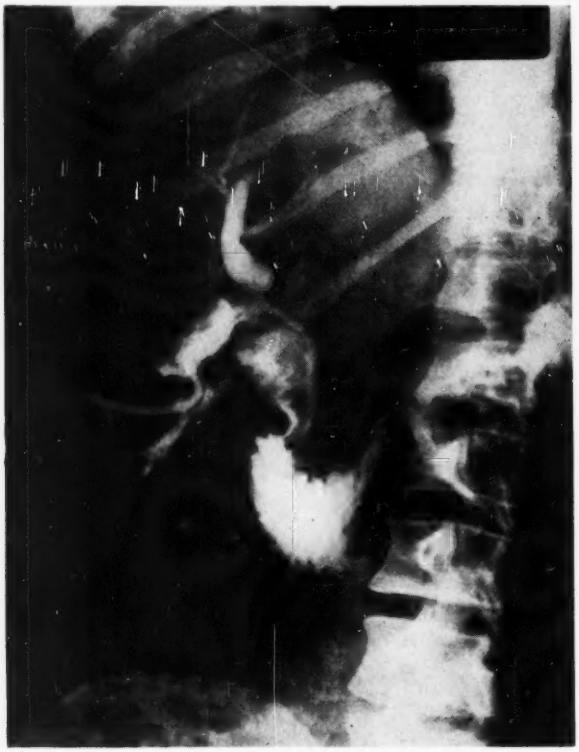

Fig. 1—Case 2. Cholangiogram two weeks postoperatively. No calculi. Dye enters duodenum readily. Tiny caliber of common bile duct is visualized as compared to excessive dilatation of common hepatic duct. Intrahepatic ducts normal.

It is to this type of "acholia" that our case report refers[1,4,11]. It is usually of poor prognosis[3,8,13,16]. Many general references to "acholia" and "white bile" appear in the literature[2,5,10]. There are, however, no case reports concerning this syndrome in the Quarterly Cumulative Index Medicus listed since 1930[18].

Case 1:—B. S., white male, aged 68, admitted to the hospital April 20, 1944 because of abdominal pain (six months) and jaundice (one month). Pruritus of one year's duration associated with diabetes was controlled by diet. Ten days prior to admission the urine was dark while bowel movements were light. There had been a fifteen pound weight loss in the previous three years. No indigestion

was present except for ten days prior to admission. No chills nor fever had occurred. Appendectomy had been done in 1941.

On physical examination the patient was markedly jaundiced. Blood pressure was 118 mm. Hg. systolic over 72 mm. Hg. diastolic. Mitral and aortic systolic murmurs were heard. Axillary, inguinal and small cervical nodes were present. A ventral hernia was present in the appendectomy scar. The liver edge was palpable. A mass was also palpated below the liver edge.

Chest x-ray was negative except that the heart was of top normal size with elongation of the aorta. Survey film of the abdomen was normal. X-ray examination of the stomach and duodenum demonstrated a small hiatal hernia and a

Fig. 2—Case 2. Postoperative cholangiogram. Interductal fistula at papilla of Vater produced at operation by trauma to interductal septum. This permits interductal reflux to occur.

deformity of the lesser curvature aspect of the duodenal cap which was believed due to extrinsic pressure.

Urine specific gravity was 1.005 to 1.025; it contained 10 per cent albumin; the sugar and acetone were negative. Blood count showed 4,900,000 red blood cells, 14.5 gr. of hemoglobin, 4,600 white blood cells with a normal differential smear. Van den Bergh was 8.0 mg. per 100 c.c., direct and indirect. Prothrombin time (Quick) was 45 per cent. Other studies revealed lipase at 0.48 units; sugar, 115 mg. per 100 c.c.; urea nitrogen, 14 mg. per cent; chlorides, 110 milli-equivalents per liter; plasma bicarbonate, 24 milli-equivalents per liter; cholesterol, 300 mg. per 100 c.c.; alkaline phosphatase, 3.3 units (Bodansky) and total proteins, 7.68 gm. per 100 c.c. (albumin 5.18, globulin 2.5). Occult blood was not present in the feces.

Clinical evaluation resolved to a suspicion of obstruction to the biliary tract possibly due to a neoplasm in the pancreas. Operation was performed on May 1, 1944. The pancreas was enlarged to twice its (vertical) diameter and its surface was very hard, irregular and nodular. There was no fat necrosis. There was no evidence of primary or metastatic, lymphatic or visceral disease. The liver was enlarged, firm and greenish.

The gallbladder was greatly enlarged. Its surface was congested and pale yellow. The wall was markedly thickened. A few pericholecystic adhesions were present. Cholesterin stones about two cm. in diameter were in the gallbladder. The supraduodenal common duct was dilated to about two centimeters in diameter.

The gallbladder contained 50 c.c. of a thin, crystal-clear, colorless fluid. The gallbladder stones were removed. The cystic duct could not be identified because of inflammatory adhesions. Bile did not enter the gallbladder.

The wall of the common duct was greatly thickened. When opened, the duct contained thin, pinkish-colored fluid. A stone was removed from the common bile duct.

Tissue excised from the wall of the common bile duct was found to be benign on histologic examination. The common duct, right and left hepatic ducts were thoroughly explored. The papilla of Vater was patulous to injected fluids.

A T-tube was placed in the common duct. Clear fluid was draining from the T-tube before the completion of the operation. A cholecystostomy was also performed.

Postoperative convalescence of the patient was satisfactory except for the absence of normal bile through the T-tube for about three weeks. Less than 50 c.c. of clear fluid drained daily. Examination of T-tube drainage during this period showed that bile acids, cholesterol and esters were absent. Only 50 mg. per cent of cholic acid was present. After May 20 the character of the bile returned to normal color and content.

During the interval between May 1 and 20 (representing the period of acholia) the patient's clinical status was adequate except for emotional depression. Urine specific gravity varied from 1.012 to 1.022. Blood counts were normal in this interval except that the white blood cells rose gradually from 6,000 to 14,000 (May 8) and gradually decreased to 10,600 (May 22). Differential smear was normal. Platelets were normal. There was no change in blood urea nitrogen levels (17 to 21 mg. per cent). Blood chlorides and plasma bicarbonate were unaltered (Table I).

Certain liver function tests, however, were found to be abnormal. The van den Bergh had been 8.0 mg. per cent, preoperatively and had been relatively constant. Postoperatively it rose. On May 4 it was 15 mg.; May 5, 20 mg. and

TABLE I

LABORATORY EXAMINATIONS DURING HOSPITAL COURSE—CASE 1

	4-21-44	5-5	5-11	5-16	5-25	6-14
Urinalysis						
Specific Gravity	1.020	1.022	1.014	1.012	1.018	1.005
Albumin	10 mg.	75 mg	neg	neg	10 mg.	neg
Urobilin	sl. tr.					
Hematology						
Erythrocytes (mill/c.c.)	4.990	5.020	5.830	5.200	5.030	4.020
Hemoglobin (gm.)	14.5	14.4	17.5	15.5	15.0	11.5
Leucocytes (per c.c.)	4600	6100	14400	12500	10600	6200
Blood Chemistry						
Sugar (mg. %)	115	93	78	113	139	82
Urea Nitrogen (mg. %)	14	19	21	17	21	15
Chlorides (mg. %)	620	604				560
Plasma Bicarbonate (vols. %) (CO_2 Capacity)	54	50	48	52		50
Cholesterol (mg. %)	300		185	278	160	
Cholesterol Esters (mg. %)	128			176	84	
van den Bergh Direct	8.0	qns	biphas	immed.	delay	delay
van den Bergh Indirect (mg.)	8.8	15 mg.	20 mg.	1 mg.	0.3 mg.	0.2 mg.
Total Protein (gm. %)	7.68	6.16	7.92	7.04	7.36	8.40
Albumin (gm. %)	5.18	4.32	4.12	3.42	3.85	5.38
Globulin (gm. %)	2.50	1.84	3.80	3.62	3.51	3.02
A-G Ratio (G:A)	1:2.1	1:2.3	1:1.1	1:0.9	1:1.1	1:1.7
Lipase	0.48	0.48				
Phosphatase	3.3		7		6.7	
Prothrombin Time	45%	45%	45%	35%	61%	61%
Other						
Bile from T-tube				50 mg. cholic acid		
Bile Cholesterol			none found	none found		
Biopsy		benign				benign

then was sustained at that level through May 13 when it began to drop to 8.0 mg. With the resurgence in bile flow it dropped by May 25 to 0.3 mg. where it remained (Table I).

Another finding of interest was that the serum globulin level, which preoperatively was 2.5 gm. per 100 c.c. and postoperatively on May 3 was 1.84 gm., rose to a level of 3.8 gm. The albumin level was unchanged. On at least one occasion there was a reversal of the albumin-to-globulin ratio due to the relative increase in the globulin fraction. This returned to normal ratio after May 20. The alkaline and acid phosphatases showed no significant change. Prothrombin time which was low preoperatively remained low until shortly after the restoration of bile flow. Thereafter, prothrombin time was normal (Table I).

In this case the three weeks' period of acholia was found to be associated with changes in liver function: (a) a slight increase in the icterus, (b) an increase in the globulin fraction of the serum proteins and (c) decrease in the prothrombin time. The abnormalities regressed after normal bile flow was re-established.

Cholangiogram (June 2, 1944) showed narrowing of the pancreatic and supraduodenal segments of the common bile duct for about three inches. It was also noted that a shadow suspicious of a retained stone was present.

Re-operation was decided as the best course for this patient because malignancy in the pancreas could not be excluded and because of the inadequate bile conduit due to the severe stricture of the distal portion of the common bile duct. Accordingly, operation was done on June 18, 1944.

Massive adhesions were present beneath the previous incision and along the course of the T-tube. The gallbladder was empty and small; its wall was very thick. The liver and surrounding structures showed no evidence of primary or metastatic malignant disease. The surface of the pancreas was hard and irregular and presented a hard, three cm. mass on its superior border about five cm. medial to the descending limb of the duodenum.

After separating the dense adhesions, the opening for the T-tube in the common duct was exposed. The wall of the duct was greatly thickened. The duodenum was mobilized by cutting its lateral peritoneal relection. The distal segment of the extraduodenal portion of the common bile duct was surrounded by very dense tissue although it was not imbedded in the adjacent pancreas. On biopsy this tissue was found to be inflammatory.

The T-tube was removed and the opening in the common bile duct enlarged. The duct was explored and cholesterin stone material about the size of a small pea was removed. A sessile papilloma about one cm. in diameter was observed immediately distal to the junction of the hepatic ducts. This papilloma represented the shadow which had appeared on the previous cholangiogram. The

papilloma was removed. (It was benign on microscopy.) The duct was then irrigated. The hepatic ducts were dilated. The common bile duct distal to its junction with the cystic duct, however, was narrow and its wall thickened. Since the previous cholangiogram had demonstrated this to be a long stricture of the distal common bile duct, no effort was made to dilate it.

The common duct was divided transversely just above the upper end of the previous incision in the duct. The distal (duodenal) end of the duct was closed with interrupted cotton sutures. A section of the indurated tissue in this area was removed for microscopic examination (benign).

The proximal bile duct was then anastomosed to the duodenum over a four cm. segment of catheter using two rows of interrupted cotton sutures.

In view of the previous serious disturbance in liver function it was deemed inadvisable to remove the atrophic gallbladder at this time.

The patient's postoperative course was normal. Gastrointestinal x-ray studies revealed barium between the anastomosis of common duct and duodenum, above the second portion of the duodenum. The patient was discharged from the hospital on July 11, 1944.

Follow-up examination in September 1952 found the patient to be well and free of any evidence of biliary tract disease.

Case 2:—M. McS., a married woman, 32 years old, was admitted to the hospital on December 1, 1951 because of abdominal pain of one month's duration. Pain was continuously present in the right upper quadrant and radiated along the flank to the right suscapular region. It was aggravated by food. Two weeks prior to admission she noted that stools were lighter than normal in color. Oral cholecystogram (10 days before admission) revealed poor function. The gallbladder was dilated and contained calculi.

Past medical history included a similar attack of abdominal pain approximately two years previously (1949). This was accompanied by jaundiced sclerae, clay-colored stools and dark-colored urine.

Physical examination demonstrated a tender mass in the right upper quadrant—probably gallbladder. Laboratory examinations revealed blood urea nitrogen of nine milligrams per cent, blood amylase of 49 (Somygi) units and an icterus index of 40 units. The blood count was normal except for a 12,000 leucocytosis. Urine concentration was normal; bile was present and urobilin was found in dilutions up to 1:40. The preoperative diagnosis was hydrops of the gallbladder secondary to chronic calculous cholecystitis. It was suspected that cholangitis was present.

Parenteral fluids and antibiotics were administered. After five days (December 6, 1951) operation revealed severe subacute infection to be present which

involved the gallbladder, adjacent colon, duodenum and common bile duct. There was a large hydrops of the gallbladder. A stone was palpated at the papilla of Vater. The common hepatic duct was greatly dilated. Incision was made into it. A small amount of colorless, mucinous fluid escaped under pressure. An ureteral catheter could be passed distally through the common bile duct for approximately three inches. Neither the catheter nor fluid injected through it could pass into the duodenum. The lumen of the common bile duct was very small (five mm.). The duct wall and surrounding tissues were edematous and thick. Bile was not present in the ducts; only clear mucoid secretion was seen.

Because the obstruction at the papilla could not be released by irrigation through the duct, the duodenum was opened by a longitudinal incision on its antimesenteric aspect. The papilla was identified. The pancreatic duct orifice was distinctly seen to empty separately from the orifice for the common bile duct. An ureteral catheter was passed from the duodenum into the common bile duct. This maneuver injured the septum between the terminal segments of the bile and pancreatic ducts.

Using transduodenal and supraduodenal approaches, the stone was removed from the common duct by manipulation and fragmentation. Fluid now readily passed from the duct into the duodenum. T-tube drainage of the common duct was used after cholecystectomy had been done for cholelithiasis.

Postoperatively, the patient became more jaundiced. Only a small amount of clear fluid drained through the T-tube. After 72 hours bile appeared through the T-tube and the jaundice decreased. There were no postoperative complications.

An indirect cholangiogram on the 14th postoperative day showed that dye entered the duodenum without delay; no stones were visualized. The diameter of the common bile duct was very small. The common hepatic duct was dilated. The intrahepatic ducts were of normal size (Fig. 1).

It was also noted that a traumatic fistula was present between the terminations of the common bile and pancreatic ducts. This had permitted reflux between the ducts (Fig. 2). No clinical symptoms were associated with this interductal reflux. The patient left the hospital after three weeks.

The T-tube was removed four months later (April 1952). During the early part of June 1952, patient noted the appearance of scleral icterus and clay-colored stools.

She was re-admitted to the hospital on June 18, 1952. At this time icterus index was 30 units while all other laboratory examinations were normal. Operation was performed on June 21, 1952. The common hepatic duct was dilated. The common bile duct could not be identified because it was atretic. An hepaticoductoduodenostomy was accomplished over a T-tube. Her convalescence was

normal. The patient was discharged from the hospital two weeks postoperatively. The T-tube was removed in December 1952. The patient is well (June 1953).

Discussion

The absence of bile (acholia) from the intestinal tract is usually associated with obstruction to the bile passages. An additional cause is the failure of the liver to produce bile. This is often a premortem event. In the cases reported, the patients recovered and are in excellent health despite hepatic failure associated with acholia.

The few reports in literature concerning acholia are vague. The etiology for and the pathology of this syndrome in which bile is not produced are obscure[2,5,10]. It is known that it appears in long-standing cases of obstructive jaundice and, usually, in patients with malignancy. It has been reported in several cases of longstanding calculous disease of the common bile duct[11].

Of similar character is the "obstructive" phase present in some 20 per cent of patients with "hepatitis"[14]. The acholia in these cases has not been satisfactorily explained. Exudate may block the periportal region at the junction of bile capillaries and ducts or there may be a rupture of this "canal" simulating the "regurgitative-reflux" mechanism. The best indicator regarding flow of bile and its production is in serial determinations of serum bilirubin, urine urobilinogen and selected liver function tests. If urine urobilinogen is low or absent and the serum bilirubin is stabilized or decreasing, it may be that acholia due to liver failure is present. This should indicate that urgent steps be taken to relieve obstruction.

Experimental evidence indicates that acholia occurs when obstruction to the bile passages and infection co-exist[2,5,10]. Infection undoubtedly accelerates the cycle in bile pigment change from pigmented bilirubin through nearly colorless biliverdin. Experimental evidence also has shown that the bile duct epithelium absorbs and excretes, dilutes and depletes the contained bile so that the residual fluid (except for calcium) becomes nearly isotonic with (blood) serum. Hence the bile in the ducts is colorless. Mucin also may be added from intramural duct glands.

Should bile not be formed, then there may be no change in the icterus index. Indeed, it is conceivable that the blood bilirubin level could decrease. This fact may fallaciously influence the prognostic value of repeated determinations of the bilirubin levels. Naturally, bilirubin formation in other reticulo-endothelial tissues must be considered in the clinical evaluation.

In the cases reported, the common bile duct was of small calibre because of chronic cholangitis, (choledochitis) and a periductal inflammation. Following surgical relief of the obstruction to the biliary tract, it took three days to three

weeks before hepatic function was restored suffiiciently to permit the excretion of normal bile. During this interval it was noted that icterus increased.

It is wise to evaluate all patients with jaundice to determine that the absence of increasing jaundice might indicate impending or actual hepatic failure rather than clinical recovery.

Such patients should be treated (a) with antibiotics, (b) by surgical drainage of the obstructed bile passages and (c) by adequate protein and carbohydrate therapy.

Whether or not the bile is permitted to reach the duodenum is not as important as the relief of obstruction. The liver cell can return to normal function after extrahepatic biliary obstruction is relieved[17]. Secondary operation can be done at a later time to reconstruct a proper route for bile flow into the intestines.

Summary

1. Acholia may occur more frequently than is indicated by sparse reports in literature. Acholia does not occur without some degree of pre-existing jaundice whether inflammatory (cholangitis or hepatitis), calculous or neoplastic.

2. Presence of white bile in the common duct usually presages imminent and absolute hepatic insufficiency and subsequent fatality (in patients with malignant disease of the bile ducts) unless the obstruction is relieved and the infection overcome. It does not necessarily carry a poor prognosis in cases associated with benign obstruction of the ducts or in patients with hepatitis.

3. Failure to form normal bile may be reflected as a decrease in the blood bilirubin level. This can alter the significance of blood bilirubin levels as a prognostic sign. It is best to correlate urobilinogen (urine) with blood bilirubin levels over consecutive days. Correlated hepatic function tests are valuable.

4. During a three week period of acholia the following changes occurred in liver function:

a. slight increase in icterus,

b. an increase in globulin fraction of serum protein,

c. decrease in prothrombin time.

These abnormalities regressed after normal bile production was re-established.

Conclusion

Patients with calculous obstruction to the common bile duct who had severe hepatic insufficiency manifested by acholia are reported as recovered.

The authors acknowledge the medical management by Dr. H. J. Tumen and Dr. H. Freiman in Cases 1 and 2 respectively.

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PRE- AND POSTOPERATIVE PROBLEMS OF THE GALL TRACT*

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Introduction

The problem of pain in the upper right quadrant, with or without jaundice, has during the past fifty years changed greatly. As first presented, the problem seemed only the simple one of a stone or stones in the gallbladder, with the simple solution of surgical removal of these stones. Today, it is recognized as a most intricate problem of diagnosis with medical and surgical treatment of multiple and complicated pathological lesions. The advances in medical therapy have not kept pace with the newer diagnostic means or diagnoses, nor with the procedures to control these conditions by surgical therapy. The emphasis in this paper is on the diagnoses which require surgical therapy.

A year ago at the Postgraduate Course of the National Gastroenterological Association, the problem of the postcholecystectomy syndrome was presented[1]. The discussion today expands the premises of last year, adding knowledge gained during the time from study of our own cases, review of the literature, and observation in a number of clinics in six European countries. The clinics specifically quoted have contributed in a particularly specialized manner to the knowledge and diagnosis of this syndrome. Only the more condensed details of the technical processes will be presented, sufficient only to demonstrate that the diagnosis and therapy to be described have been established by precise methods.

The Medical Approach to Gall Tract Problems

Contributions to diagnosis and treatment from a purely medical viewpoint during the past year have not been extraordinary. It is interesting that several studies by internists have established diagnoses and therapies which are substantially surgical. A year ago we made the following approach to the problem of gall tract diagnoses by describing the following differential[1]:

TABLE I

Differential Diagnoses of Gallbladder Disease

1. Coronary Disease
2. Gastric diseases: neoplasm, gastritis, peptic ulcer
3. Duodenal diseases: diverticula, infection, ulcer
4. Pancreatic diseases: neoplasms, infection, calculi
5. Renal diseases: neoplasms, infection, calculi
6. Liver diseases and hyperemia
7. Vagotonic imbalance intestinal disturbances

*Read before the Eighteenth Annual Convention of the National Gastroenterological Association, Los Angeles, Calif., 12, 13, 14 October 1953.

8. Appendicitis
9. Peritonitis
10. Retroperitoneal tumor
11. Spinal arthritis

In addition, we have since found cases of gastric mucous membrane prolapsed through the pylorus, and a diabetic crisis of neurosyphilis, both confused with gallbladder disease.

Diagnostic Tests

There are still a multitude of laboratory procedures employed; an average of 24 appeared in the charts of one European clinic. Such multiplicity suggests that none of these procedures are altogether satisfactory.

The cephalin flocculation tests with the alkaline phosphatase test as a group, appear the most dependable. Routine tests generally cover much the same ground, and in my opinion can be simplified to six tests taken from a single specimen of 10 c.c. of blood, a technic already reported and developed at the New York Medical College.

The value of blood iron studies is yet to be confirmed. High serum iron values are evidence against posthepatic blocking with jaundice. This may prove helpful in the future, but at present iron blood studies are still confused and of little value.

Caroli's studies[2] of the time of bromsulfathaline excretion through a transduodenal tube and the quantitative amount of the excretion are subject to so many errors and variables that they warrant little confidence. Studies made along similar lines by the author were discarded as inaccurate some time ago.

Medical Treatment and Diseases of the Sphincter of Oddi

Although most of this paper is devoted to discussion of the surgical diagnosis and treatment of gall tract diseases, some comment should be made here about the treatment, medically, of diseases of the sphincter of Oddi.

Hypotonia of the sphincter of Oddi can be so perfectly controlled by surgical means to be outlined later, that a dearth of medical treatment need not distress us. Hypertonia of the ampulla of Vater (biliary dyskinesia), the explanation of which as a clinical entity can be established positively, merits the use of antispasmodic drugs: atropine, nitroglycerine, aminophyllin, and sedatives such as phenobarbital. Intravenous injections of dehydrochlorate of soda may be helpful. The high fat diet (egg yolks beaten in cream) is in order. This was also employed for years in the empirical olive oil treatment.

Diathermy is particularly stressed at the University of Lausanne. A most complete and scientific approach to the treatment of biliary distress both pre- and postoperatively was evidenced in the work at the Lausanne University which we observed last summer. The spas of Europe still flourish and are helping in

the treatment of functional conditions of the biliary tract by increasing fluid intake with their waters, increased exercise, and a "regimen"—as their diet is called. Adequate diagnostic study was lacking in many spas which we observed. Organization and scientific study should be employed in place of the inadequate routinism in the medical work of these world famous spas.

The greatest contributions to the problem have been made by two French investigators. One of the contributors has been Dr. Caroli, of St. Antoine's Hospital in Paris. It is interesting to note that he has made so many contributions to gallbladder disease, as an internist. All through Europe he is known as the one medical man who thinks like a surgeon. His studies of the biliary tract have developed surgical diagnosis and surgical practice tremendously. He is said to be the only medical man in the world to dictate to the surgeon what pro-

TABLE II

CLASSIFICATION OF BILIARY DUCT DISEASES

A. Functional duct diseases
   1. Hypotonia of sphincter of Oddi
   2. Hypertonia of sphincter of Oddi
B. Organic duct diseases
   1. Lithiasis
   2. Inflammatory lesions: papillitis, Odditis, or Mallet-Guy disease
   3. Neoplasms
      a. Of the ducts
      b. Of the sphincter of Oddi
   4. Pressure on ducts from without: e.g., enlarged glands, neoplasms, diseases of adjacent organs
   5. Anomalous duct structures
   6. Parasites within the ducts
C. Pancreatitic diseases
   1. Pancreatitis
      a. Acute
      b. Chronic
   2. Neoplasms of the pancreas

cedure is to be instituted. This takes strength, for he cannot, like the surgeon, during an operation, alter his course to suit a new development but must stand by his premises. He is thus always in a precarious position.

The second contributor has been Dr. Mallet-Guy of Lyons. He, on the other hand, is a surgeon with most complete laboratories, both chemical and radiographic, in his two hundred bed surgical pavilion and operating theater. Here is the reverse of the medical man, a surgeon with a medical mind and complete medical equipment. His animal and other experimental studies, exhaustive in character, are conducted in the laboratories at the University of Lyons.

SURGICAL DIAGNOSIS OF BILIARY DISEASES

It has been repeatedly demonstrated that even the most thorough exploration of the common duct, at the time of surgery, will not always reveal intra-

ductal lithiasis. Lahey[3] and others[4,5] have variously estimated the incidence of common duct disease associated with gallbladder disease. It may be as much as 38 per cent[4]. These associated duct diseases include: lithiasis, sphincter of Oddi diseases, and various other conditions which we will discuss and which are outlined in the classification given in Table II.

The Technics of Surgical Diagnosis of Biliary Diseases

The detailed technics of Mallet-Guy have been published elsewhere[4]. Most of the European Clinics which we visited, used technics similar to his. They are as follows:

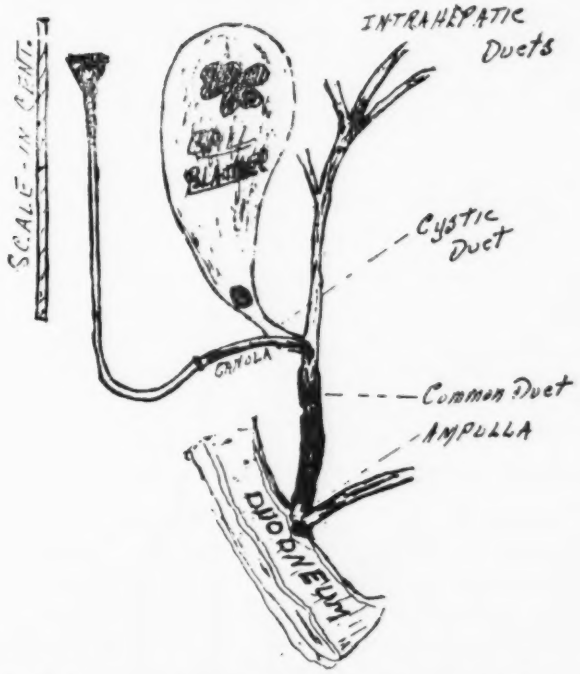

Fig. 1—Method of manometric and cholangiographic filling of the common duct.

Anesthesia:—No preoperative medication may be used. Local or even nitrous oxide-ether oxygen may be employed, since these drugs do not disturb or alter findings. Pentobarbital will not affect findings.

Examinations:—Two independent examinations are made, the findings must be correlated and must be in accord in order to establish the diagnosis.

The first is the manometric examination. Normal saline is injected through an especially designed trocar at the terminal point of the cystic duct, four or five mm. above its junction with the common duct. Ten c.c. of solution are instilled and the pressure taken. Then another 10 c.c. are instilled and the

pressure taken again, and the procedure repeated a third time. Three times is the minimum, but the study may be repeated up to the injection of a total of 60 c.c. Normal pressure, after the injection through the cystic duct is 8 to 14 centimeters of water, or if the injection is through the gallbladder, 14 to 18 centimeters. Higher pressures, of course, mean obstruction at some point in the ductal system, and pressure below eight centimeters has a physiological significance. Pressures are recorded by a revolving manometer or read as fluid levels, as in an ordinary barometer. The cystic duct is rarely found occluded and almost never totally obstructed.

Fig. 2—Method of filling ducts and measuring pressure.

After taking the pressures, the second type of examination is done. Ten c.c. of lipiodol are injected for cholangiography and a film taken. This is repeated at intervals of a few minutes for a minimum of three injections and three films, and in some clinics up to as many as 20 to 24 films are taken. Mallet-Guy uses a small pencil spot-light above the table to indicate the exact spot which is to be filmed. This method reveals disease states of the gall tract which would produce postcholecystectomy syndrome in 38 per cent of cases if overlooked[1]. Thus, over one-third of cases requiring removal of the gallbladder have pathology other than that of the gallbladder alone.

These simple technics were used in most of the clinics we visited, but Caroli in Paris, has elaborated the procedure even further. Under the operating table is a compartment where the roentgenologist can lie supine. From this position he checks fluoroscopically the injection drop by drop as it fills the ducts, and by telephone or loud speaker, he orders the films exposed at the right moments. Thus, he can isolate any particular area for study, note any alteration in the progress of the injected material, and see that spot films are taken at any point of interest. A complete operating theater of this sort has also been installed at the American Hospital at Neuilly.

Though placing the cannula in the cystic duct is the most satisfactory way of studying the ducts, it has disadvantages. No information is gained about the gallbladder, and if the cystic duct is injured, the gallbladder must be removed. The sphincter of Oddi cannot be studied with injection through the gallbladder unless the pressure of the sphincter of Oddi is greater than the valves of Heister, and even then, the study is not accurate.

Albot of the Hotel Dieu in Paris, has evolved diagnosis of spasm of the cystic duct and other pathological processes of the gallbladder by complicated gallbladder pressure studies.

Spasm may occur either in the gallbladder alone, or in the sphincter of Oddi alone, or both may occur in the same patient. In these instances the less common process of filling through the gallbladder is performed. But most problems of the gallbladder alone can be solved by manual and visual examination. When the abdomen is opened and there is obvious pathology of the gallbladder, manometric and film studies are made. The films are processed while the gallbladder is being removed and are ready to be viewed then, no time being lost.

The welfare of the patient whose abdomen must be opened after a previous cholecystectomy is greatly improved by this method, for only the stump of the cystic duct need be identified, the cannula inserted, the procedure carried out and the diagnosis arrived at. There is no difficult and traumatizing surgery or complete dissection of the ducts needed to discover what situation has to be faced.

Should this method seem too time-consuming and complicated at first sight to us Americans, with our desire for speed and rapid action, let us stop and at least give credit to these men and to the methods which they have developed, for in no small measure they have clarified diagnosis and treatment of problems of the upper right quadrant. It is far better to take multiple films while the abdomen is open than to do injurious and difficult surgical intervention. These methods, in a great measure, eliminate a multitude of secondary operations. With the abdomen open, transduodenal duodenectomy and biopsy, or opening the common duct are among the operations that may be necessary.

In reading the films of operative radiography, if there is a question of differentiation between an enlarged gland and a stone within the duct, first search is made for the gland and the gland removed. A second set of films is

then made at once and if the shadow has disappeared, the differential diagnosis is complete. Thus, the extremely dangerous procedure of forced intraductal probing is eliminated, and with it the all too real danger of false passages or blind perforations. One more blind surgical procedure is eliminated.

Before considering the various ductal lesions in some detail, which may be diagnosed with the aid of the above described technics, some statements about the sphincter of Oddi and the indications for removal of the stoneless gallbladder should be made.

The Sphincter of Oddi

Ample studes have established the anatomical identity of the sphincter of Oddi. Not only have the original statements of Oddi been substantiated concerning a sphincter at the end of the common duct, but at the Hospital Edouard Herriot at Lyons, it has recently been established by exhaustive histological studies that in addition to a sphincter of Oddi at the terminal portion of the common duct there are accessory sphincteric fibers at the union of the common duct with the duct of Wirsung, and at the terminal portion of the latter duct. In addition, Ivy with his 16 different types of pathology of the sphincter of Oddi[6], has firmly established this structure as a physiological entity.

Removal of the Stoneless Gallbladder

We feel that in 100 per cent of cases of gallbladders containing stones, removal of the gallbladder is indicated. The stoneless gallbladder, however, should be removed only on five indications.

1. Obstruction of the cystic duct
2. In typhoid carriers
3. In chronic pancreatitis
4. In carcinoma or other tumor of the gallbladder
5. Cholesterolosis, (a form of cholelithiasis, actually).

Removal of the stoneless gallbladder causes a marked aggravation of hypotonia and produces an immediate relaxation of the sphincter of Oddi. Then a reflux into the duct of Wirsung occurs and it is a definite cause of secondary pancreatitis.

Cholecystectomy is never performed *alone* in the better clinics of Europe. All cases are studied for pathology of the common ducts and of the sphincter of Oddi and pancreatic disease immediately after the abdomen is opened. Manometric and cholangiographic studies are done in all cases.

Biliary tract surgery is regarded in Europe as very delicate, and is entrusted only to the most experienced surgeons, the heads of clinics. The combination of manometric and radiographic studies in the hands of such men results in many

fewer cases of postcholecystectomy syndrome among their statistical reports. The exact diagnosis has been significantly aided by the development of the manometric and radiographic examination. As a result of this method there is less trauma to the patient and less injury to his tissues, in addition to an accuracy of diagnosis beyond any previous methods employed.

Acute Cholecystitis

The question of early or late operation for cholecystitis has occupied much space in medical literature during recent years. Full discussion of the problem cannot be undertaken in this paper, but perhaps you will agree with me that the following facts are evident and axiomatic:

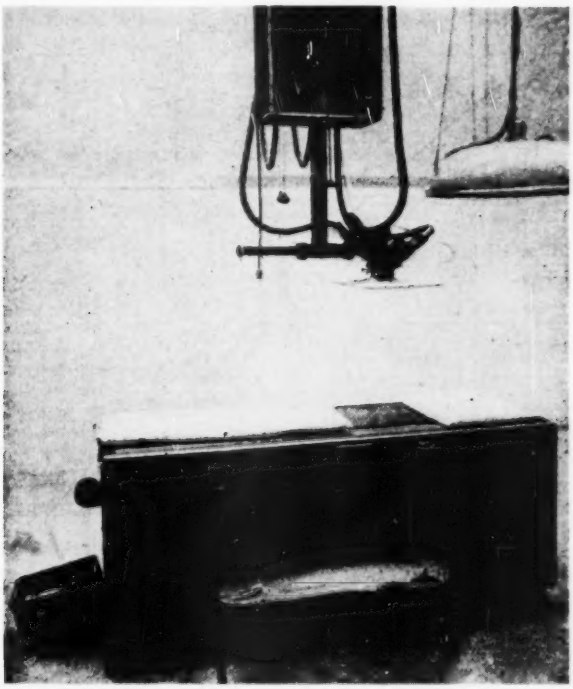

Fig. 3—Operating and radiographic table with observer beneath.

1. The trend in recent years has been toward early operation for acute cholecystitis.

2. Perforations are rare and rupture of the gallbladder even more rare.

3. The problem is not identical with that of appendicitis and is in no way parallel.

4. Residual common duct pathology is very frequent in acute cholecystitis. Thirty-eight per cent of cases of gallbladder disease also have duct pathology, necessitating secondary operation[4].

5. Adequate ductal surgery is usually difficult, and is not attempted in most cases of acute cholecystitis.

Over one-third of the cases will need re-operation after surgery for acute cholecystitis. Every clinic we visited told us of a similar experience: "An acute abdomen opened; right rectus; appendix normal, which had been in question; acute cholecystitis discovered; the gallbladder removed; following recovery, almost immediate return of the upper right quadrant pain.

Let me quote from George B. Eusterman, in his discussion in a recent Yearbook of Medicine, on the subject of cholecystectomy[7]. "The practitioner is also

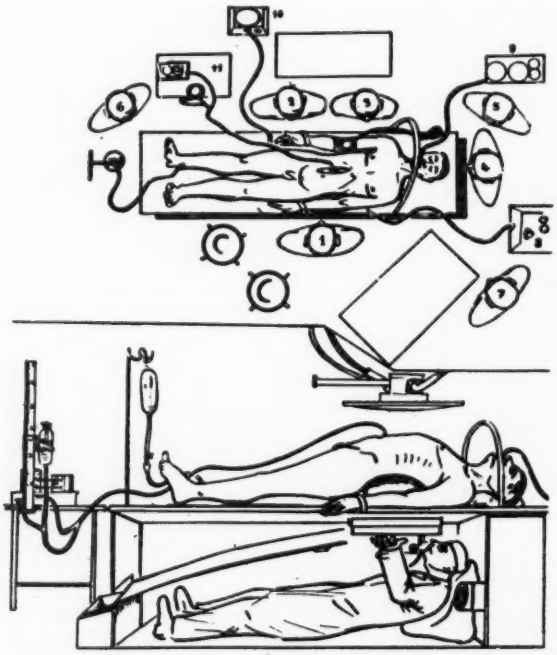

Fig. 4—Arrangement of Paris operating table (Caroli).

concerned about the possibility of injury to the extrahepatic ducts, which is a real tragedy and still occurs too frequently. Only a minority of patients are operated on by highly experienced and skilled surgeons; general practitioners and occasional operators attend to the majority. The danger is in removing instead of draining the gallbladder, especially if the anatomic features are not distinct, and it is surprising to know that many surgeons feel it necessary to remove the gallbladder in every case of acute cholecystitis. When serum amylase determinations are done routinely following severe biliary colic, it is surprising how often the pancreas is found to be acutely involved. Many surgeons feel that this is justification for delaying operation until the inflammation has subsided".

Mustard has expressed his feelings on the management of acute cholecystitis by stating that what is needed is an "aggressive conservatism"[8].

As a result of these observations the following rules have been established in most of the institutions visited:

1. Every effort should be made to carry the acute case of cholecystitis through to a period of subsidence of symptoms, so that when operation is undertaken adequate ductal studies and ductal surgery can be done.

2. If the case appears to be progressive, with a rise in temperature, increase in leucocyte count and increased peritoneal irritation with upper right quadrant rigidity, the procedure is cholecystostomy.

3. Cholecystostomy for acute cholecystitis, if operation is found necessary, is through a vertical right rectus incision under local anesthesia, with simple tube drainage. Then 14 days to three weeks later the abdomen is reentered through

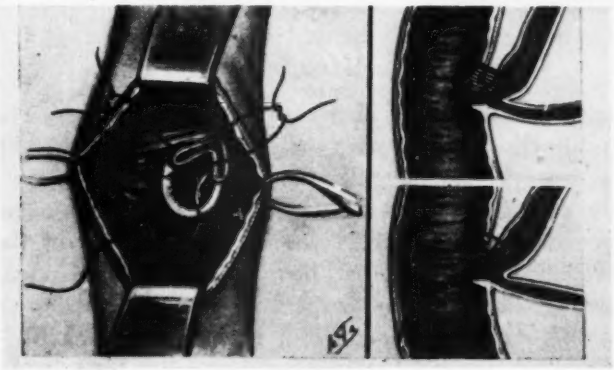

Fig. 5—Technic of transduodenal sphincterotomy.

a subcostal incision (which is outside the area of adhesions) and an accurate study is made of the process. Common duct surgery can be done at this time. By far the greater number of cases can be carried to the delayed or interval operation, so that only one operation is necessary. Louvain University is in favor of the delayed operation, routinely.

At Louvain there is a reluctance to use antibiotics for acute cholecystitis lest they mask the progress of the case, alter blood counts and local symptoms, and thus lead to a false sense of confidence. In general, however, in Europe, antibiotics are used, not only in massive doses, but also in multiple products. The use of two antibiotics seems to be routine.

Operative Technic:—The flap method of Mallet-Guy of Lyons, requires a U-shaped incision from below the ensiform process slanting to the right for six or seven inches, to almost the level of the navel. It then turns to the right and gradually rises to the rib border at the anterior axillary line. This results in an extraordinary exposure and greatly facilitates operative procedures. There is

no increase in healing problems, and no greater incidence of postoperative hernia than when other incisions are used.

Mallet-Guy has said: "As long as medicine and surgery of the gall tract is solely based on clinical history, physical examination and manual findings at operation, the results will often be imperfect and there will be a high percentage of recurrences"[4].

Any cholecystectomy, even with an opening in the common duct, may leave unrecognized lesions of either inflammatory, anatomical, or functional nature, with resultant pain, distress, or even postoperative fistula. Opening the common duct without study of the sphincter of Oddi may lead to postoperative residual symptoms, even when the duct is studied by catheterization and dilation.

A general discussion of the biliary tract diseases with special attention to their diagnosis by the surgical means previously outlined, and also to some newer surgical treatments, follows.

Hypotonia

Hypotonia is usually a part of a constitutional diathesis. The primary type is usually found in the visceroptotic type of individual, weak, asthenic, with low blood pressure, anemic and mentally depressed. The secondary type is always present in acute cholecystitis and after removal of the stoneless gallbladder; with it occurs a secondary pancreatitis. Hyotonia allows reflux of the bile into the pancreatic duct, and concomittantly allows reflux of the duodenal content into the bile duct. By roentgenography, the pancreatic duct is usually seen to be elongated and dilated with evidences of secondarily thickened walls, after a very short period.

Symptoms:—Distress is less acute than the usual distress of gallbladder disease; the pain is rather a soreness, not of a colicky type. There is pressure at once after meals over a large area, with alternating attacks of diarrhea and constipation, intolerance of fats with ensuing diarrhea, psychosomatic disturbances, anxiety, depressions, migraneous attacks, diabetic changes with endocrine changes in the pancreas, and also changes in the external secretions of the pancreas. The subjective symptoms are not characteristic.

Diagnosis:—Diagnosis is established by finding diminished pressure in the common duct and a rapid opening of the sphincter of Oddi, and an immediate spilling into the duodenum of the lipiodol. The sphincter is seen to be wide and relaxed or abnormally dilated. The diagnosis can be proved at once on the operating table by injection retroperitoneally of the right splanchnic nerves with novocaine; if the tonus of the sphincter returns at once, there is no organic disease.

Treatment:—Right splanchnicectomy is specific. Results have been verified by repeated use by a large number of European surgeons.

Hypertonia

The clinical entity of hypertonia is well established in Europe, but it is interesting to note that apparently a diagnosis of hypertonia is a rarity in American medicine.

Diagnosis:—There is pain in the epigastrium, or upper right quadrant. It resembles a gallbladder attack of minor intensity, is colicky in nature, and is accompanied by nausea and vomiting. Pain is most likely to appear later in the digestive period rather than immediately after meals. This pain is not a feeling of fullness. It occurs usually in a hyperesthetic type of person with migraine, and a hurried nerve-complex irritability.

The problem of papillitis will receive attention later in our discussion, but it must be mentioned here from the point-of-view of differential diagnosis. Injection of a quick-acting antispasmodic, such as nitroglycerin, will lead to quick relaxation of the spasm in a case of hypertonia. This is diagnostic. There will be no effect in a case of papilloma. Amyl-nitrite also can be used to relax spasms.

Treatment:—Treatment consists of antispasmodics: atropine, belladonna, nitroglycerin and aminophyllin. High fat diet, exercise and general hygiene are also indicated. Phosphate of soda in the morning is helpful. Injection of novocaine through a duodenal tube will also be effective. Banthine is also effective, as is splanchnic nerve secretion.

Surgical Therapy:—There should be no intraductal bougie therapy, even using the slightest force, and no surgical therapy by way of the ducts if medical means are unsatisfactory. After due consideration, a transduodenal approach to the sphincter is in order and a dilation may be done, or a sphincterotomy done with direct vision, as shown in (Fig. 5).

The sphincterotomy of Doubiliet appears to be a blind and ill-advised procedure. The sphincter may be dilated and a T-tube placed in the common duct protruding into the duodenum beyond the sphincter. There is a disadvantage in this treatment in that among 25 per cent of cases there is regurgitation of intestinal fluids into the biliary tract so that the tube must be removed.

Choledoco- or cholecystoduodenostomy is often used at the Basel clinic of the Burgh Hospital. The doctors there are most emphatic in their opinion that ascending infection has been no problem. Kjergaard[9] has reported excellent results with no cholangitis or other complications. Observations at a number of clinics indicates that where there was dissatisfaction with the use of transduodenal procedures on the sphincter, it was due to lack of routine drainage.

Papillitis—Primary Idiopathic

Odditis:—The muscular tone of the sphincter has been studied alone for several years. More recently it has been definitely established that organic

changes may also take place in the muscle and that fibrosis may occur in the papilla[10].

These changes have been established by biopsy and microscopic study and two types appear to exist. Symptoms are the usual ones of dysfunction of the papilla and are not specific. They may, however, be severe enough to result in a life of painful invalidism. They follow the already mentioned gall tract pattern.

When manometric and radiometric examination has shown pathology at this point, on opening the duodenum a characteristic finding will be seen. The sphincter prolapses into the duodenum, and is readily identified as a round, protruding area like a minute cervix uteri. The diagnosis is confirmed by biopsy. There are two possible forms: hyperplasia following fibrosis, and hyperplasia by cystic form.

Treatment:—There are now two mistakes which must be avoided: one, to do nothing; the second, to remove a functioning gallbladder. The proper procedures are: choledocoduodenostomy, transduodenal sphincterotomy, or choledocojejunostomy with use of drain after the duodenostomy. Complications and fistulae do not occur if a drain is used. There is a school who do not believe in the approach through the duodenum, but in my opinion, (after study of some of their cases), this is due to the fact that they have not used a drain after operation, but close the wound up tight.

Papillitis—Secondary

The following facts have been established:

1. The diminution in intramural caliber is due in part to an increase of external muscle and in part to thickening of the mucus membrane.

2. The papilla is definitely a zone of sphincteric fibers.

3. The papilla is a zone of reduplicated mucous membrane.

4. The papilla is a zone of extreme infectibility.

5. The papilla is the zone that regulates the mechanism of pressure in the biliary tract.

Various types of papilla have been verified in the pathological laboratory, but the distinctions are too fine to consider from a clinical standpoint.

Clinically, papillitis is evident in two forms: one form is pseudoneoplastic and resembles cancer and is extrabiliary, lying at the head of the pancreas; the second resembles calculi impacted in the common duct.

The history is variable and the symptoms slow in development and in gravity. There is an enlarged liver, and manometric radiographic examination

evidences obstruction, and diagnostic changes in the terminal portion of the common duct appear in the radiograph consisting of little protrusions on the sides of the duct, which resemble very small multiple diverticula.

Differential Diagnosis:—Hypertonia is evidenced by spasm, and increased pain with also increased pressure, which do not appear in papillitis; the diverticulous effect in the duct is also absent in hypertonia.

Carcinoma may necessitate transduodenal approach and biopsy for diagnosis. Cancer may be suspected because it usually produces more complete obstruction causing difficulty in passing the sphincter even with high pressure; antispasmodics are of no value in relieving the obstruction in cases of cancer. While the spasmodic element accompanies a papillitis, it usually gives way under the influence of a strong antispasmodic.

Treatment:—Treatment consists in resection of the papilla in part or whole, using T-tube drainage with the terminal portion of the tube in the doudenum. Choledocojejunostomy or cholecystogastrostomy may be the operations of choice, but blind sphincterotomy is definitely contraindicated.

Carcinoma of the Papilla of Vater

Mallet-Guy has said, "There is probably no location in the human body save perhaps in the nervous system where a malignant tumor so small is capable of causing such severe symptoms as does carcinoma of the papilla of Vater".

The radiological appearance is very characteristic. The duct is not materially dilated, and the terminal portion has a dimpled appearance with projections at the two sides of the duct with an indentation in the center. Hess, at Basel, states that at times there is a narrowing at the end resembling the filling of a glove finger. Manometric pressures are very high, up to 50 c.c.

None of the clinical signs taken alone are characteristic. Increased icterus, pain, increased fever and general symptoms in the region are suggestive. The disease is never recognized before jaundice sets in with chills, fever, feeling of pressure after eating, vomiting, alternating diarrhea and constipation, and especially diarrhea after eating fats. Previous periods of pain ranging over several years are also suggestive. A dilated gallbladder is the most important sign; it is more likely to be greatly dilated than in cancer at the head of the pancreas. Intestinal hemorrhages are a strong diagnostic sign. Icterus becomes very green and deepens, and at intervals the stools become colored and duodenal drainage reveals bile.

Remissions are of a temporary nature, lasting as much as a month at a time. Drainage through a duodenal tube may yield cancer cells or even a piece of tissue for biopsy. Symptoms may not be characteristic, but they do demand operative investigation.

In differential diagnosis from lithiasis, it will be noted that periods of fever are more often present in cases of cancer than in those with lithiasis. Pain in cancer lasts for longer periods than does pain of lithiasis, and periods of icterus in lithiasis may occur which are less intense than those occurring in cancer.

Angiocolitis is rare as a primary condition in carcinoma of the ampulla, but it may be present as an accompanying condition. There is more likely to be an enlarged liver and gallbladder in cancer of the pancreas. In prolonged catarrhal icterus there is less enlargement of the liver and gallbladder. Fibroadenoma of the papilla is less likely than carcinoma to produce complete stenosis of the papilla, and while both are likely to have a long history, that of fibroadenoma is not intermittent.

These points of diagnosis are suggestive, but again the manometric and radiographic method is the only way to achieve completely accurate differentiation. This should be followed by transduodenal approach to the sphincter and biopsy with rapid-frozen section examination, which is confirmed later by fixed slide examination[11].

When studied by manometric and radiometric methods, it is observed that papillary carcinoma causes dilatation of the common duct and gallbladder, but that the terminal portion of the common duct is filled in a normal position, and that it is narrowed and funnel-shaped, rather than wide and square and blunt as occurs with carcinoma of the pancreas. Hess of Basel likens the filling in carcinoma of the papilla to the narrowing caliber at the end of a glove finger (an inverted funnel). Pressure is elevated in both conditions, and may be as high as 60 mm. of saline.

Acute Pancreatitis

Acute pancreatitis is universally acknowledged to be a nonsurgical disease. In addition to intravenous work, withholding of food and giving of antibiotics, paravertebral block is the most successful procedure.

Chronic Pancreatitis

In France there has been very complete study of the organic and functional states of the biliary tract in chronic pancreatitis using the manometric and radiographic method[12].

In the course of chronic pancreatitis, attacks of the biliary tract are shown by painful crises which have been demonstrated to be pure gallbladder colics. Later, as the inflammation continues in the pancreas with retention of biliary contents, cholangitis ensues, and often there is evidence of narrowing of the biliary tract. Stones may also occur. All these may be present, but still findings by the Graham method of cholecystography will be normal, and findings by duodenal tube study may vary only slightly from normal.

According to these studies cholangiographic findings may be divided into two classes[12].

Type 1:—This type is characterized by dilatation of the biliary tree above the pancreas and stoppage of the dye in a conical form at the upper border of the pancreas, giving rise to a curve of the duct which the Swiss refer to as the "swan's neck" elongation of the duct. Pressure must be raised to fill the retropancreatic ducts, and they appear rigid with parallel borders or with a wavy outline. The sphincter of Oddi is always atonic and dilated, and there is no reflux into the duct of Wirsung. The manometric findings complete the diagnosis without error, for the pressure only needs to be raised to overcome the delay in filling the ducts. Differential diagnosis in relation to cancer with adenopathy is usually apparent.

Type 2:—Clinically this type is characterized by painful attacks radiating to the left side of the abdomen, periodic digestive disturbances, pressure after meals, and endocrine changes in the pancreas or external pancreatic secretion deficiency. Dilatation of the ducts is only moderate, with a round globular appearance particularly in the retroperitoneal part of the ducts. The sphincter of Oddi is closed, and there is greatly augmented resistance to pressure in the ducts, and reflux into the ducts of Wirsung with marked dilatation of the canal. This pancreatitis is secondary to sclerosis and stenosis of the sphincter of Oddi. It resembles pancreatitis induced by impacted stone at the sphincter of Oddi or cancer of the head of the pancreas.

A few thoughts on the exact position of the secretin test are in order. In acute pancreatitis apparently the pancreatic secretion returns rapidly to normal in the majority of patients within the first week of illness. When abnormal secretion is found, there are no diagnostic criteria upon which a definite diagnosis can be established. Thus, the secretin test has limited practical value in the diagnosis of acute pancreatitis. By the time the test can be performed the pancreatic responses to secretin are likely to have returned to normal ranges. Here a negative test is of no diagnostic value. Positive findings may, on the other hand, be of great importance. This is particularly true if the secretin test is performed after the subsidence of clinical signs and symptoms. In such a case abnormal secretion is suggestive of the persistence of pathology and the likelihood of the development of chronic pancreatitis. In fact, the secretin test may help in diagnosis of chronic pancreatitis to a great extent. In chronic pancreatitis there is persistent marked abnormality of pancreatic response, with marked lowering of bicarbonate concentration in the fluid aspirated from the duodenum. The volume response and amylase secretion reponse are affected to a lesser degree. Secretin stimulates bicarbonate function more than enzyme function.

Treatment:—Treatment of the first type where the sphincter of Oddi is dilated, consists of left splanchnicectomy or splanchnicotomy. The treatment for Type 2, calculus pancreatitis, is to remove the stone. It must be stressed

from a study of clinical cases that the pain of pancreatitis is quite as frequently in the right side of the abdomen as in the left.

Another European clinic divides chronic pancreatitis into three types.

Type 1:—Cholecystopancreatic type. In this type manometric readings are above 15, and according to cholangiography there is compression to the point of stenosis in the inferior part of the common duct. The edges of the duct are dilated and stiff-walled with a "swan's neck curve" of the main duct, and dilatation of the main duct. Symptoms are those of the bile duct syndrome with inferior costal pain. The treatment is cholecystectomy or cysticoduodenostomy.

Type 2:—Chronic pancreatitis with hypotonia of the sphincter of Oddi causing reflux into the duct of Wirsung. It is cured by right splanchnicectomy. The premise that all regurgitations into the duct of Wirsung are due to spasm as presented by Doubillet and Mulholland, and that the routine treatment is sphincterectomy, is refuted by manometric and radiographic studies. Treatment is surgery of the sphincter by transduodenal approach and not by blind intraductal sphincterotomy. In exceptional cases plastic repair of the sphincter may be indicated.

Type 3:—Chronic relapsing pancreatitis. The clinical history is one of a series of recurrent painful epigastric episodes, the pain radiating to the left. The treatment is left splanchnicectomy. Partial gastrectomy is too radical an operation for this condition, and is not necessary since the results of splanchnicectomy are satisfactory. In calculus pancreatitis, as mentioned before, the stone is removed.

Carcinoma of the Pancreas

X-rays show a characteristic high stenosis, with the terminal filling of the duct, blunt and wide, and the end of the duct dilated, and a dilated common duct and also the dilated gallbladder of Courvoisier. If they fill, as they do only in rare cases, the pancreatic ducts are narrow and never dilated. Manometric pressures are high, with a limit of 50 or 60. If there is a common duct block, jaundice is absolute, but in the case of a common duct which does not penetrate the pancreas, none of these signs are present. The manometric and radiographic method is practically the only method other than biopsy which will differentiate carcinoma of the papilla of Vater from carcinoma of the head of the pancreas. This diagnosis is most important, for increasingly, the Whipple operation of radical resection of the pancreas is being discarded because of its high mortality and because it shows so little ability to lengthen the patient's life. Anastomosis only, may help to prolong a not uncomfortable life. Again let me state, the radical Whipple operation of pancreatic resection has such a high mortality and the after-effects are so poor, that the operation has been discarded for a simple short-circuiting operation, the results of which give longer life and less suffering. Carcinoma of the papilla of Vater can, of course, be resected.

If the results of denervation of the hepatic artery and the relief of hepatitis, particularly the symptom of pruritus, are found to be consistently true and are verified in a larger group of human beings, a new palliative procedure of great worth has been established. Mallet-Guy's extensive surgery on dogs has firmly convinced him of the merits of the procedure. Also in small groups of patients where he employed hepatic artery denervation in jaundice of not over four months' duration, he found almost immediate relief from the intense pruritus of the jaundice. Thus a new approach is given to the difficult problem.

Stones Overlooked at Previous Operation

We will not stress the applicability of manometry and radiographic study to diagnosis of this situation, since the value of the method will be at once apparent. In a previous article, the author emphasized the occurrence of intrahepatic stones and the recurrent formation of stones in the intrahepatic ducts with later transition to the common duct[1].

It was a conception that was in the minds of many of the clinic groups seen this summer, and the opportunity has been present to verify the recurrence of stones in the common duct after removal of the gallbladder, with complete common duct studies. The technical procedure is injection of only a small amount of lipidol at a time, lest a larger dose overlie the stone and obscure its shadow. As has been demonstrated by Nissen, it is axiomatic that 10 per cent of common duct stones give no symptoms.

Operative Trauma, Severed Duct

Here, these diagnostic methods have an unchallenged appeal, as only the stump of the duct need be identified for filling purposes so that the presence of injury can be established. This is also true of ducts that have become invloved in postoperative adhesions.

Pressure from Without on the Ducts

In a case of lymphosarcoma pressing on the ducts which we saw last winter, laboratory findings varied every day, at one time suggesting extrahepatic jaundice, and another time intrahepatic jaundice. Cancer of the duodenum may also cause pressure. Pancreatitis and pressure from carcinoma of the pancreas have already been discussed.

Anomalies and Intrahepatic Duct Stricture

Diagnosis of anomalous biliary ducts is impossible by any other methods. The common duct was shown in one case we saw this summer, to be separate from the duct of Wirsung and to go to the right above the pancreas to enter the duodenum. This is merely a medical curiosity. Other anomalies may easily be demonstrated by operative cholangiography.

Parasites

Though rare, parasitic causes for biliary obstruction do occur. We may mention Ascarides; Hydatid cysts may also rupture into the extrahepatic or intrahepatic ducts, or may make pressure against the ducts.

Reformation of Gallbladder

That the cystic duct stump syndrome[13] may in effect become a reformation of the gallbladder, was demonstrated when an abdomen was opened by Nissen at a European clinic this summer. A previous case history with pathological reports, including gross description and slides, had established the fact that the gallbladder had been removed. On opening the abdomen, to the surprise of the surgeons, a perfectly normal size gallbladder was demonstrated and removed.

Carcinoma of the Biliary Ducts

Carcinoma may occur in intrahepatic ducts, or at the junction of intrahepatic and extrahepatic ducts, which is more frequent. Carcinoma of the common duct itself, is the least infrequent. The persistent obstructive symptoms of this pathology demands surgical exploration.

Summary

1. In this discussion there has been an attempt to further clarify and classify the pathological processes that give rise to the postcholecystectomy syndrome and their appropriate solution.

2. The technic of manometric and cholangiographic correlated diagnosis has been presented.

3. Pathologic identities have been presented as established by manometric cholangiographic studies.

4. A rational approach to the problem of treatment of acute cholecystitis has been presented.

5. The evils resulting from the removal of the stoneless gallbladder have been stated.

6. The sole indications for the removal of stoneless gallbladder have been enumerated.

7. The treatment of hypotonia of the sphincter of Oddi by right splanchnicectomy, has been endorsed.

8. The medical and surgical treatments of hypertonia of the sphincter of Oddi have been enumerated.

9. The applicability of left splanchnicectomy for pancreatic lesions has been advised.

10. The denervation of the hepatic artery in prolonged jaundice and intractable pruritus has been suggested.

11. The exact diagnosis and treatment of the postcholecystectomy syndrome has been codified.

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THE MEDICAL TREATMENT OF PEPTIC ULCER WITH A NEW ANTICHOLINERGIC COMPOUND*

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Introduction

The etiology and cure of peptic ulcer remains an insoluble enigma. The modern concept[1] of pathophysiology has confined the formula to an emotional psychogenic charge which explodes through the dorsal vagal nuclei and nerves to activate acid peptic erosion in a susceptible mucous membrane on a selective anatomical site. Following the clinical successes with methantheline bromide[2,3] numerous anticholinergic compounds have been synthesized[4,5,6] capable of safely suppressing gastric secretion and motility with minimal toxic effects.

This investigation was undertaken to evaluate the therapeutic response of a new anticholinergic preparation, Compound 14045‡, on the clinical course of peptic ulcer.

Chemistry and Pharmacology

Chemically, Compound 14045 is 1-cyclohexyl-1-phenyl-3-pyrollidino-1-propanol methsulfate. It is a white, stable, bitter, crystalline substance, which like Banthine, is a quaternary ammonium compound.

Pharmacologically it is a potent and dependable parasympathetic blocking agent by effectively inhibiting neural stimuli at those ganglia and effectors where the presence of acetylcholine mediates transmission of stimuli. Laboratory and clinical pharmacology indicate the agent has a profound inhibiting effect on intestinal motility and upon the flow of gastric, pancreatic and salivary secretions. Intravenously it is more toxic than atropine but orally, compound 14045 is about equal in toxicity to atropine. Ingelfinger and Machella found little or no blurring of vision or dryness of the mouth at the 100 mg. level. When administered intragastrically by Kirsner and Palmer[5] in doses of 25 to 175 mg. anacidity appeared in one of eleven patients with moderate side-effects developing in 10 of 13 patients. As is the case with other potent anticholinergic drugs, however, there is a marked variability in individual clinical response and tolerance to the side-effects of the drug[7]. The most characteristic toxic responses to these compounds are xerostomia, mydriasis, constipation, disturbance of urination and tachycardia.

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‡Supplied by Eli Lilly & Company.

TABLE I

TREATMENT OF PEPTIC ULCER WITH COMPOUND 14045

No.	Case	Age-Sex	Diagnosis	Oral Dosage (mg.)	Side-effects	Results
1	WA	28–M	Duodenal Ulcer	200	None	Good
2	RH	53–M	Duodenal Ulcer	200	None	Good
3	KB	13–M	Duodenal Ulcer	200	None	Good
4	GL	30–M	Duodenal Ulcer	200	None	Fair
5	ER	53–M	Duodenal Ulcer	200	Xerostomia & Vomiting	Fair
6	LB	28–M	Duodenal Ulcer	200	None	Good
7	AF	73–M	Duodenal Ulcer	200	None	Good
8	AN	70–F	Duodenal Ulcer	200	Xerostomia	Fair
9	JN	40–M	Duodenal Ulcer	200	None	Good
10	FK	48–M	Duodenal Ulcer	Discontinued after 4 Mo.	Nausea, Vomiting & Constipation	Poor
11	RS	36–F	Duodenal Ulcer	200	Xerostomia & Mydrosis	Fair
12	GL	45–M	Duodenal Ulcer	200	None	Good
13	JP	37–F	Duodenal Ulcer	200	None	Fair
14	RD	63–M	Duodenal Ulcer	200	None	Good
15	PS	43–M	Jejunal Ulcer	400	Xerostomia	Poor
16	WK	46–M	Duodenal Ulcer	200	Xerostomia	Good
17	PU	42–M	Duodenal Ulcer	200	None	Fair
18	HO	49–M	Duodenal Ulcer	300	None	Good
19	HR	37–M	Duodenal Ulcer	200	Mydrosis	Good
20	BB	34–M	Duodenal Ulcer	200	None	Good
21	GS	46–M	Duodenal Ulcer	200	None	Poor
22	MW	45–F	Duodenal Ulcer	200	None	Poor
23	AN	44–M	Duodenal Ulcer	200	None	Good
24	JR	23–F	Duodenal Ulcer	200	None	Poor
25	TS	61–M	Duodenal Ulcer	250	Xerostomia	Good
26	JK	45–M	Duodenal Ulcer	200	None	Good
27	WE	38–M	Duodenal Ulcer	200	None	Good
28	BH	75–M	Duodenal Ulcer	250	None	Good
29	TV	37–M	Duodenal Ulcer	250	None	Good
30	CC	–M	Duodenal Ulcer	300	None	Good

Continued administration or decreased dosage will usually raise the individual tolerance.

Clinical Trial with Compound 14045 in Peptic Ulcer

A consecutive series of 30 roentgen proven cases of peptic ulcer, of which 29 were chronic duodenal ulcer and one jejunal ulcer, were selected for ambulatory treatment with Compound 14045 administered in doses of 50 to 100 mg. every six hours for a period of eight months. We were primarily interested in the rapidity and degree of symptomatic improvement, as well as any evidence of toxicity which might occur. In addition, a restrictive ulcer diet with milk feedings between meals, antacids and supplementary vitamins were employed in the therapeutic management. Tobacco, alcohol and coffee were totally prohibited for the duration of the investigation. The intentional selection of this type of case permitted an apparent pathological common denominator and

TABLE II

Summary of Results

Diagnosis	Poor	Fair	Unsatisfactory	Good	Satisfactory	Toxic Reactions	Percentage of Reactions
Duodenal Ulcer	4	6	10 (34.4%)	19	19 (65.6%)	7	7 (24.08%)
Jejunal Ulcer	1		1 (100%)			1	1 (100%)

a serious challenge to the therapeutic effects of Compound 14045. All patients were observed regularly and the clinical response recorded, but no attempt was made to compare this drug with other anticholinergic compounds. Secretory and motor determinations were avoided in this series since the parasympathetic blocking effects have already been established. Because side-effects seldom appeared below the 100 mg. dose, we chose, at the beginning of treatment, to administer 50 mg. every six hours and later to increase the nocturnal dose to 100 mg.

In Table I the age-sex category revealed 24 men from age 13 to age 75, and 6 women with ages ranging from age 23 to age 70. This ratio of 4:1 compares favorably with the universal sex incidence for duodenal ulcer. The highest dosage, 400 mg. daily, was used in the patient with a penetrating jejunal ulcer, while in all but five others, 200 mg. per day in divided doses was regularly

administered. The summary of side-effects and final results is best noted in Table II. The results were unsatisfactory in 10 (or 34.4 per cent) of the patients with duodenal ulcer and in one (100 per cent) in jejunal ulcer. Satisfactory results occurred in 19 (or 65.5 per cent) of the cases with duodenal ulcer. This latter group experienced complete and sustained relief of ulcer symptoms for eight months, while those with the unsatisfactory response, epigastric pain, distress or indigestion persisted or quickly recurred while under treatment. The large jejunal ulcer crater observed roentgenologically at the start of this program was larger eight months later in spite of 100 mg. of Compound 14045 every six hours. Other investigations[8] using related compounds observed total relief of symptoms in jejunal ulcer.

Toxic reactions were observed in 7 (or 24.08 per cent) of the patients with duodenal ulcer and in 1 (or 100 per cent) in the patient with jejunal ulcer. Xerostomia was observed in six and mydriasis in two of the seven patients manifesting toxic reactions. Nausea, vomiting and constipation was very evident in one case but at no time was urinary retention or tachycardia reported.

Comment

The therapy of peptic ulcer should rest on a rational explanation of the etiology and pathogenesis of the disease even though gaps in this knowledge have been an obstacle to progress in treatment[9]. Adopting these basic concepts[1] to the medical management, an attack on the vagus nerve with anticholinergic autonomic blocking agents would appear to be desirable. The mechanism of pain in duodenal ulcer has long been a subject of much controversy. In all probability it results from multiple factors (secretory, motor, inflammatory) acting singly or in combination[10]. The pharmacologic studies, both in laboratory animals and in man, together with clinical observations in patients, indicate that Compound 14045, when administered orally, is effective in inhibiting gastric motor and secretory activity. Our results in the treatment of peptic ulcer with Compound 14045 indicate that the drug could be administered orally in effective doses over a prolonged period of time and caused a minimum of side-effects. Our success or failure with Compound 14045 was determined primarily by the amelioration of symptoms and the lack of recurrence of symptoms at a time when recurrence would be expected. We include complete and significant relief as satisfactory therapy, and no relief, intolerance to the drug or recurrence of symptoms while on adequate dosage as unsatisfactory. Our clinical impression is that there is definite acceleration of healing of the ulcer crater while under treatment with Compound 14045.

Because of the wide variation in reaction to emotional stress in individual patients, it becomes necessary to make these adjustments in dosage selectively. The dosage schedule should apply during the active stage of the disease and for a considerable period thereafter because in all probability the primary factor for the disease still exists after healing or improvement has occurred. Increase in

dosage to the therapeutic level is advisable particularly during periods of unusual stress or intercurrent illness.

Since this study was not controlled with other medication, and since the therapeutic regime contained dietary and antacid substances, no final conclusions are warranted regarding its absolute status in therapeutic potential.

Side-effects describe the reactions of a drug which are incidental to its administration and not the effect primarily sought. In some degree they are an accompaniment of all therapy involving potent anticholinergic agents, as well as many other drugs, and they represent a pharmacologic action on organs not primarily concerned with the disease under treatment.

Dryness of the mouth and throat and blurring of vision are the most common subjective manifestations of parasympathetic inhibition. As might be anticipated, toxic reactions appeared more often and were pronounced with larger doses particularly when 200 mg. per day was exceeded. As the toxic levels were approached with the larger doses symptomatic response improved and patients preferred the evidences of vagal inhibition to the ulcer distress. In considerable overdosage a curare-like action may occur since it is a true anticholinergic compound. No such manifestations of this type, however, have been observed or reported in our series.

Summary and Conclusions

1. A new anticholinergic agent, Compound 14045, was combined with the routine ulcer management of 30 patients with roentgen proven duodenal and jejunal ulcer in divided doses of 200 to 400 mg. every 24 hours.

2. The results were unsatisfactory in 10 or 34.4 per cent of the patients with duodenal ulcer and in 1 or 100 per cent of the patients with jejunal ulcer. Satisfactory response occurred in 19 or 65.6 per cent of the patients with duodenal ulcer for the observation period of eight months. No better results could be expected by increasing the dose in the majority of patients who failed to respond satisfactorily.

3. Toxic effects were noted in 7 or 24.08 per cent with duodenal ulcer and in 1 or 100 per cent in the patient with jejunal ulcer.

4. Compound 14045 can be administered orally in the treatment of peptic ulcer in effective doses over a prolonged period of time and provokes minimal side-effects. This latter characteristic permits increased dosage which ultimately improves the therapeutic effect.

5. This new anticholinergic compound is a valuable adjunct in the modern medical management of peptic ulcer.

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Discussion

Dr. Davis (Van Nuys, Calif.):—I wonder if anyone has tried using more than one of these anticholinergic drugs in small doses, or in combination, and noted the same effect with lesser side-effects?

Dr. W. Ostrow (Brooklyn, N. Y.):—I would like to know whether the Doctor has informed his patients that this was a new drug which they had not received previously? The reason for this question is the oft resultant impression upon a patient with new therapy, and this becomes a form of psychotherapy.

Dr. Michael W. Shutkin (Milwaukee, Wisc.):—It was quite evident to the patients that this was a clinical investigation, and there was no way of concealing the simple fact because the drug was administered to them with that explanation. Obviously, they were curious enough to inquire about the new drug, and I could in no way neutralize or alter their psychological attitude to this fact.

Dr. H. L. Chris (West Hollywood, Calif.):—Thinking along this line I had a patient recently whom the neurosurgeon thought had cerebral sclerosis; I performed a sympathectomy upon her. I wonder if a medical sympathectomy with this drug would affect the cerebral vessels and help this patient?

Dr. Burwell:—Who prepares this drug? Is it on the market yet?

Dr. Shutkin:—Eli Lilly & Co.

Dr. McFarland:—I would like to ask if any of the patients in this series had previously used older anticholinergic compounds and whether they found them superior to this new drug.

Dr. Joseph Shaiken (Milwaukee, Wisc.):—I wonder if Dr. Shutkin wouldn't say a few words about the indications for the use of anticholinergic compounds. These drugs have created a lot of criticism and I think the main difficulty has been the average man's ignorance of their indications. I mean particularly their place in the management of peptic ulcer.

Dr. Shutkin:—We all recognize this to be a most timely subject. Peptic ulcer is constantly with us; it is man's broken defense against time and stress.

In answer to the first question, I have no experience with the effect of anticholinergic drugs in cerebral dilatation. We ourselves have not observed the curare-like effects that have been described in the literature due to overdosage. McHardy and Browne reported a curare-like effect with Banthine. In our experience, we have never attempted such huge dosage.

To answer the second question, I must candidly confess to you that this drug in the group of anticholinergic compounds used today, is not as effective pharmacologically and clinically as some of its predecessors. The satisfactory response in 65.4 per cent is not adequate therapy. Very good medical treatment carried out determinedly and persistently, in a cooperative patient should give no less than 90 per cent good results. I recognize that this statement would likewise provoke comment, but I am not including in this group of patients the intractable ulcers, for these are best treated surgically. For the sake of discussion, we have, in our teaching, always emphasized that 50 per cent of duodenal ulcers would generally get well with a minimal type of treatment, 40 per cent become the chronic group, and 10 per cent eventually are treated surgically. The latter are the group with the complications of hemorrhage, obstruction, perforation and intractable ulcer.

The indications for the use of anticholinergic compounds is a very timely question. Like drugs before and after, there is use and misuse. The patient with an upper gastrointestinal syndrome, typical of pain-food-relief, etc., and without a roentgenological examination to establish the diagnosis, is often given an anticholinergic drug and a soft diet, whatever that means. Patients with chronic duodenal ulcers are conditioned towards obstruction by (1) edema, (2) spasm, and (3) fibrosis, and are readily thrown into acute pyloric obstruction with promiscuous use of these drugs. To make it crystal clear, the anticholinergic compounds are definitely contraindicated in the medical treatment of duodenal and gastric ulcer, whenever there is evidence of obstruction. Obviously, this requires a roentgenological examination and vomiting in itself is no indication of obstruction. The most satisfactory result of anticholinergic therapy in medical practice today is its direct inhibition upon gastric and motility secretion.

THE CLINICAL IMPLICATIONS OF MUCOSAL PROLAPSE THROUGHOUT THE ALIMENTARY TRACT*

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Gastrointestinal causes of abdominal symptoms have by no means been exhausted. Much remains to be clarified with reference to evaluating chronic distress in the alimentary tract. The possibility is strong that clinical entities not at present within our knowledge may emerge in the future. The vast number of cases of functional gastrointestinal disorders which are treated on a rather empiric basis attest eloquently to our limitations.

A probable cause of hitherto unexplained symptoms has been looked for in recent years in the concept of the independent movement of the mucosa of the stomach, small and large bowel. While the major interest has centered on benign mucosal prolapse of the stomach, the clinical implications of detached mucosa elsewhere in the gastrointestinal tract merits consideration. This presentation will attempt to summarize the present fund of accumulated knowledge on this subject and supplement this with our clinical observations of the past five years.

We have recently reported on the clinical, roentgenologic and gastroscopic features of benign gastric prolapse[1] and have been further impressed, as a corollary, with the problems in differential diagnosis[2] which it has created in lesions of the pyloroduodenal juncture. Interest in the concept of redundancy and detachment of mucosa has also broadened so as to include a search for this phenomenon at other points of stress and at sudden shifts in the pressure gradients at various levels of the gastrointestinal tract. Attention has therefore been directed to the cardio-esophageal juncture, the stoma in the postgastrectomy state, the ileocecal valve, the rectosigmoid juncture and the rectum and in areas in which an artificial change in pressure is effected i.e. ileostomy and posterior gastroenterostomy.

The concept of the independent movement of the mucous membrane of the digestive tract is not a new one. Forssell[3] reported extensively on this as early as 1923 and concluded from his studies based on anatomic and roentgenologic data and in the living subject that the mucous membrane of the stomach, jejunum and ileum normally and rapidly underwent continuous motion produced by the muscularis mucosa in which the outer coats of the intestinal wall did not participate. He speculated on the possible pathologic states this phe-

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nomenon might induce if it became abnormally overactive. In 1948, experimental corroboration of the independent motility of the gastric mucosa was reported by Brooks et al[4]. He and his co-workers showed, by serial roentgenograms of the dog's stomach made after marking the curvatures with lead shots and the muscularis mucosa with thorotrast in the submucosa, that the shot representing muscularis propria remained relatively fixed while the mucosa changed position.

Benign Prolapse of Gastric Mucosa

Benign prolapse of the stomach mucosa implies redundancy of the gastric mucosa at the antrum with herniation of the rugal folds into the base of the duodenum. The diagnosis is based purely on roentgenologic criteria of the presence of a smoothly rounded defect occupying the base of the duodenal cap although we have encountered the phenomenon gastroscopically in the form of prominent and redundant folds which spilled through to the pyloric ring and new folds reformed at the angulus with each new peristaltic wave. The lesion is often transient and changeable[5].

The correlation of this phenomenon with clinical symptoms has not been clearly established but where symptoms are present the relationship is suggestive. At one extreme it has been reported in 18 per cent of routine gastrointestinal x-rays in asymptomatic individuals[6] and at the other extreme by other authors it has been deemed of sufficient importance in many cases to be treated surgically by means of excision of the redundant mucosa or more recently by subtotal gastrectomy since recurrences have taken place following pyloroplasty[7].

Speculations as to etiology have ranged from chronic irritation and inflammation with the consequent loss of the independent stretching mechanism of the mucosa to hypertrophy of the pylorus. Noteworthy in our series was the high associated incidence of gastric hypertrophy as well as coincident gastrointestinal disease (peptic ulcer, cholelithiasis). Cardiac and nutritional disturbances have been mentioned as predisposing factors. Gastroscopically, we visualized the actual prolapse in nine cases. Our experience has led us to attach great importance to the concomitant occurrence of stress and anxiety which may predispose to hypermotility.

Clinically the patients were predominantly in the older age groups. The symptoms when present were not clear cut or typical but isolated attacks of localized epigastric distress associated with nausea and vomiting simulating pyloric obstruction ("ball-valve syndrome") have appeared in specific cases to be related to states of increased nervous tension. The possibility that these represent exacerbations of functional gastrointestinal distress must be kept in mind. Hemorrhage occurred in a sufficient number of our 60 cases (22 per cent in our series) and is often massive enough so that this phenomenon may well be included in the list of possible causes of upper gastrointestinal bleeding. This brief consideration of the clinical manifestations of benign gastric prolapse might

well be concluded with the remark that the frequent presence of peptic ulcer and hypertrophic gastritis complicates the exact evaluation of the complaints. Isolated attacks of pain in the upper abdomen which coincide with roentgen evidence of exacerbation of prolapse lend weight to a casual relationship especially when, in remission, such cases present a normal stomach roentgenologically.

When a diagnosis of benign prolapse is established and symptoms are present the clinician is faced with the necessity of a logical therapeutic program. The treatment is essentially that as for peptic ulcer i.e. bland diets, sedation, antacids, antispasmodics and attention to relief of emotional tension and stresses in life situations. The complications of prolapse have been treated as have been the complications of peptic ulcer and they present similar problems in clinical judgment. Recurrent hemorrhage, intractability to medical management, pyloric obstruction and the probability of prepyloric malignancy have been indications for surgical intervention in ours and other reported series. Excision with pyloroplasty has been the most widely used surgical approach although it would appear that recurrences which have followed this type of surgery would make subtotal gastrectomy the most definitive procedure[8]. In seven of our cases operated upon and followed for a period of three years to one month results were good in four, vomiting persisted in one, recurrence occurred in one and in another the result was undetermined, so that the efficacy of surgery appears still to be evaluated.

Differential Diagnosis of Benign Gastric Mucosal Prolapse

The roentgenologic criteria for the diagnosis of benign gastric prolapse appears to be sufficiently clear-cut but we have become alerted to pitfalls in its diagnosis as our interest in this condition has progressed. Instances have occurred of other conditions, both benign and malignant, which first presented themselves as benign prolapse. These have been, in order of their frequency, gastric polypi with long pedicles acting with a ball-valve mechanism, secondary lesions from carcinoma of the pancreas and the colon to the duodenum, primary prepyloric carcinoma, hypertrophic gastritis, multiple gastric adenoma, duodenal ulcer, pylorus when x-rayed over the spine.

These cases were confirmed by autopsy, surgical exploration, peritoneoscopy or repeated gastroscopic examination. They emphasize the need for a high level of suspicion and for the use of every diagnostic measure at our disposal including exfoliative cytologic studies when a roentgen interpretation of benign gastric mucosal prolapse is made. The following clinical case report exemplifies the problem in differential diagnosis created by this x-ray diagnosis.

Case 1:—A white male (E. R.), age 68, was admitted with cramping pain in the right lower quadrant of the abdomen and right subscapular region for 5 months prior to the first interview. A painful tender mass was palpated in the right upper quadrant of the abdomen. The roentgenologist reported thickening

and stiffening of the mucosa of the greater curvature of the pyloric end of the stomach. In addition a mushroom-like defect at the base of the bulb was noted, typical of the roentgen-ray changes seen in prolapse. Gastroscopic examination revealed the presence of an extramucosal infiltration into the posterior wall in the distal half of stomach. The mucosa was thick, nodular and rigid. Operation revealed an adenocarcinoma of the ascending colon with invasion to the small bowel, duodenum, and adjacent anterior abdominal wall. A wide resection with an ileotransverse colostomy was performed. Death occurred two months later from metastasis.

Prolapse and Retrograde Extrusion of Gastric Mucosa Into the Esophagus

Since the cardioesophageal juncture is another point of a sudden shift in the pressure gradient, retrograde prolapse of the gastric mucosa into the esophagus might be expected. Wells reported the first such case[9] by esophagoscopy in 1947 where the herniated gastric mucosa appeared as a polypoid mass and produced obstruction at the lower esophagus to the passage of the instrument. The differential diagnosis rests between hiatus hernia, esophageal varices, pedunculated gastric malignancy, retention of barium in the lower esophagus. It is probable that many such cases have been confused with these and that the actual incidence of esophageal gastric prolapse may be higher.

Based purely on roentgenologic data, Feldman[10] reported two such cases in 1951 and regarded the condition as a clinical and roentgenologic entity. He showed roentgenograms illustrating the mushroom-type of filling defect in the lower esophagus at the head of the barium column as it meets the mass of gastric mucosa extruding in a retrograde manner. Esophageal gastric prolapse has also recently merited attention in the field of pediatric roentgenology[11].

The following summary of one of Feldman's cases illustrates the clinical manifestations and the roentgenologic criteria which obtain in a typical case:

A white female, aged 60, complained of epigastric distress, heartburn, sour regurgitation, nausea and vomiting. Her symptoms were worsened after eating. Following cholecystectomy, intermittent upper abdominal pain persisted radiating to the back. Gastrointestinal fluoroscopic study showed a reflux of barium into the esophagus due to esophagogastric relaxation. A sliding knuckle could be seen extruding into the lumen of the lower esophagus accompanying the reflux of barium. This was observed only in the prone position. Intermittent retroperistalsis was accentuated during vomiting or regurgitation. Roentgenograms showed the prolapsed gastric mucosa rising in a mottled mass into the lumen of the lower esophagus.

In another similar case, the extruded shadow disappeared when the patient was examined in the erect posture. While surgical and pathological confirmation

was not obtained, it was felt that these roentgenologic and esophagoscopic criteria were sufficiently definite. Increased alertness by clinicians may increase the reported number of cases.

Postgastrectomy Mucosal Prolapse

It is of interest that cases of severe gastric mucosal prolapse into the jejunum have been noted following subtotal gastrectomy in the treatment of ulcer and also following attempts to treat benign gastric prolapse by a similar surgical approach. In the latter case, the recurrence of the condition at another point attests to an underlying constitutional predisposition, probably a tendency to excessive abnormal hypermotility. Recurrences following the operation for prolapse by pyloroplasty[8] have occurred and have been used as an argument in favor of subtotal gastrectomy as the surgical treatment of choice in prolapse. Not only has the roentgen diagnosis of gastric mucosal prolapse through the stoma in a caudad direction occurred but the retrograde passage of detached jejunal mucosa into the gastric stump has also been noted. The following illustrative clinical case summary of such an intussusception of jejunal mucosa through the stoma is of interest:

Case 2:—A 41 year old male (E. J. H.) admitted December 23, 1951 had a history of a gastric resection for duodenal ulcer in 1949 and came in complaining of epigastric pain. He was an alcoholic. Roentgenograms showed the gastric resection and a well functioning stoma. At gastroscopy, the stomach segment and stoma were well visualized. Peristalsis caused undulating movement and herniation of small intestinal mucosa of the afferent loop through the stoma. The gastric mucosa showed patchy adherent exudate, edema, granularity and increased redness. Impression: (1) Postoperative superficial gastritis. (2) Herniation of small intestinal mucosa of afferent loop through the stoma. (Case through courtesy of Stephen J. Stempien, M.D. seen at the Long Beach Veterans Hospital, California).

Retrograde Duodenal Prolapse

We have observed one other form of mucosal prolapse which deserves a place in the general consideration of this phenomenon. This concerns the retrograde protrusion of duodenal mucosa up into the antrum. This phenomenon appeared to us on one occasion during a gastroscopic examination in the form of a giant doughnut-like formation of smooth duodenal mucosa which, with relaxation of the pyloric sphincter, returned to its original position.

This experience has been corroborated by Schallenberger (personal communication) in whose case there was noted the presence of a concentric series of small hemorrhagic erosions in the antral mucosa at the site of the pressure points of the prolapsed duodenal mucosa.

Ileocecal Prolapse of Mucosa

Hawley and Mithoeber[12] in 1950 described two cases of defects at the ileocecal valve closely simulating tumor which proved to be marked prolapse of ileal mucosa into the cecum. Rigler and Lasser[13] in the following year reported prolapse of the lower lip of the ileocecal valve backward into the terminal ileum. As Hinkel[14] stated "we are still in the process of learning about the many deviations from normal which may be encountered at the ileocecal valve"[18].

Hinkel presented two cases of presumable ileal prolapse which were surgically explored and stated that in 21 out of 23 large ileocecal valve defects studied roentgenologically he felt that the defect was either the result of the valve itself or of ileal prolapse. Among the causes of filling defects at the ileocecal valve may be listed: normal but conspicuous ileocecal valve, pericecal and retrocecal adhesions, retrocecal mass, posterior implantation of ileum on the cecum, a common ileocecal wall, a large ileocecal valve due to edema, hypertrophy, fatty infiltration or tumor of the valve lips and finally invagination or prolapse of normal or abnormal ileal mucosa through the valve. Fleishner and Bernstein[15] have reported extensively on roentgen-anatomical studies of the normal ileocecal valve.

In the past three years we have encountered cases of ileocecal defects reported roentgenologically as probable prolapse of ileal mucosa through the valve. Two of these reached operation and in one the prolapsed mucosa was demonstrated at cecostomy and it is interesting to note that our experience paralleled that of the others in that the microscopic diagnosis was lipoma of the ileocecal valve. These cases as well as a consideration of ileocecal valve defects in general will be reported in greater detail. It is of interest that in one of our cases, an ileitis was reported by the roentgenologist in association with the prolapse. This association has been encountered by other observers[16] although Hinkel found no associated ileitis in five cases with ileocecal defects in which he undertook a specific search for it.

The following cases reported in detail elsewhere[17] will illustrate our experience with this condition:

Case 3:—B. M., age 59, female, was admitted September 8, 1950 with gastrointestinal complaints for many years. Six months prior to admission she noted pain in the right lower quadrant radiating to the back not related to food or bowel movements. In September 1950, the entire gastrointestinal tract was normal by roentgenological study including the terminal ileum and by barium enema. Cramping pains, watery diarrhea, bilateral lower abdominal tenderness were also prominent. On July 10, 1950, roentgenograms of the colon were reported as "On the medial aspect of the cecum, exactly in the position of ileocecal valve, a small rounded filling defect was encountered the appearance of which strongly suggests prolapsed mucosa into cecum. The remote possibility of a small benign tumor cannot be ruled out". Three weeks later the same findings were reported

on a repeated examination. On September 11, 1950, an operation was performed. At surgery the ileocecal region could be palpated and the polypoid structure within the cecum was found. A cecostomy was performed and the prolapse of the ileocecal valve was demonstrated. The prolapsed mucosa was amputated and the mucosa and submucosa was repaired. Microscopic diagnosis: Ileocecal valve in which there is increased submucosal fatty tissue. Diagnosis: Lipoma of ileocecal valve.

Case 4:—L. G., white female, aged 65, with lower abdominal complaints had a barium enema performed on November 29, 1950. Within the cecum a slightly irregular, rather poorly defined filling defect was seen. With additional barium and increased pressure, the defect appeared to be at the ileocecal valve. Multiple spot films also showed suggestive evidence of a smooth rounded filling defect in the cecum. An oblique view of the cecum following evacuation showed the suggestive evidence of a mass projecting into the cecum at the ileocecal valve. When pneumocolon was induced, fluoroscopic and roentgen examination failed to disclose evidence of a filling defect or the previously suspected mass at the ileocecal valve.

An upper gastrointestinal tract x-ray five days later showed the barium had reached the hepatic flexure of the colon and an oblique film again showed suggestive evidence of a defect similar to that seen at the time of the barium enema. With compression when examined fluoroscopically at 5 hours, the defect at the ileocecal valve was again seen and in addition, there appeared to be an abnormality of the ileum approximately 6 cm. from the ileocecal valve. This portion of the ileum failed to fill completely and the mucosal folds appeared to be displaced laterally.

Multiple compression spot films again showed the concavity projecting into the lumen of the cecum at the level of the ileocecal valve and suggestive evidence of an intraluminal mass in the medio-superior wall of the ileum, approximately 6 cm. from the ileocecal valve. The possibility of localized ileitis with an inflammatory mass could not be ruled out. "The defect at the ileocecal valve may be the result of hypertrophy of the lips". A pneumocolon was performed 10 days later: "A moderately prominent ileocecal valve was seen with the barium filled and with postevacuation films. There was no evidence of an intrinsic lesion in the distal ileum or the cecum". Again two months later a barium enema was performed and no positive evidence of a lesion in any portion of the colon or the terminal ileum was seen when compared with the previous films.

Comment:—The variability of the lesion at the same examination, its visualization at later studies and again its disappearance two months later is in favor of the presence of prolapse. The variability of the defect in the ileum is also worthy of comment.

Case 5:—E. S., a white female, aged 59, was admitted with pain in the right upper quadrant of the abdomen. Her weight had been stationary and there had

been no change in bowel habit. An operation was performed on May 1, 1949. A cecotomy was performed and revealed a prolapse of mucosa from the ileum for a distance of 2 to 3 cm. without any other evidence of any other tumor formation. The mucosa was injected but otherwise was not unusual except for its polypoid appearance. The redundant mucosa was excised and the cecum was closed. Gross pathological report: "9 cm. strand-like segment of fatty tissue not unusual in cross-section". Microscopic report: "Pedunculated polypoid lesion consisting entirely of fatty stroma and lined on the surface by colonic mucous membrane. At one edge a small fragment of ileal mucous membrane is seen. Diagnosis: Lipoma of ileocecal junction".

Rectal Mucosal Prolapse

The phenomenon of partial rectal mucosal prolapse is one with which proctologists have long been familiar. This must be sharply differentiated from complete prolapse or procidentia in which the entire rectal wall participates. The high incidence of partial prolapse (loosening of the mucosa alone) is commonly encountered in daily proctologic practice and is associated with large internal hemorrhoids but in addition the rectal mucosa may be frequently mobile at the eight or ten inch level in the presence of rectal polyps at times to the extent of causing a change in the relative position of the polyp from 1 to 4 cm. from one examination to the next. An awareness of this is necessary in the search for polyps which may notoriously shift in position on separate occasions.

It has been postulated that the disturbance in motility and abnormal spasm present with hemorrhoids predisposes to rectal mucosal prolapse. We have observed instances of ballooning out of rectal mucosa into the sigmoidoscope in the region of the rectosigmoid juncture. The high percentage of partial prolapse has been attributed by some to the attendant presence of cryptitis, hemorrhoids and a short anal canal, all of which may be predisposing factors in the production of redundant rectal mucous membrane.

The following case report illustrates the clinical importance of concealed rectal mucosal prolapse as a cause of melena:

Case 6:—A four year old white male was seen in October 1948 at the Cedars of Lebanon Rectal Clinic because of bright red bleeding by rectum with bowel movements six months previous to the first interview. The child was physically normal. Repeated sigmoidoscopic examinations were negative until during one examination the patient began to cry and bear down. As the sigmoidoscope was withdrawn, a prolapse of rectal mucosa presented itself, beginning at the five inch level and extending toward the outlet for a distance of two inches. The tip of this prolapse had the appearance of a cervix and became intensely injected. There was no frank bleeding, but when the injected area was wiped with an applicator, a serosanguinous discharge was present on the applicator tip. (Case through the courtesy of Jack Kahn, M.D.)

Comment

Since it has been demonstrated that detachment of gastrointestinal mucosa does occur in animal and man at points other than excessive stress, it is conceivable that clinical symptoms may occur if the degree of the loosening is severe enough and of sufficient duration and it may well be that some cases of abdominal pain of undetermined origin may find its basis in this phenomenon. It behooves the worker in experimental medicine and the internist to add to our knowledge in the future in this regard by an awareness of its likelihood.

That mucosal detachment may be an expression of long standing sustained states of hypermotility and abnormal hypertonicity is suggested by the clinical studies of mucosal gastric prolapse. Recent studies in gastrointestinal motility and the influence of simulated emotional situations and periods of life stress as well as the effect of sympathicomimetic and anticholinergic drugs on motility and tone may prove fruitful in this connection. More refined experimental technics in this field hold promise of developing hitherto undisclosed data.

The established presence of mucosal detachment with consequent prolapse at points of sphincteric control raises a new clinical problem in the differential diagnosis from known pathologic states in these areas. It is likely that the diagnostic implications of this phenomenon may loom just as importantly in this regard as in the symptom-complexes which may emerge as a result of its presence.

As in every new advance in diagnosis or treatment, the concept of prolapse raises more questions than it supplies answers. A consideration of gastric mucosal prolapse in a given case calls for a review of the clinical picture and the more widespread use of every available measure to exclude polyp, primary or secondary malignancy of the pyloroduodenal juncture and gastritis. A filling defect at the ileocecal valve which appears inconstantly demands the abundant use of pressure spot films in differentiating from a normal anatomic variation, hypertrophy of the valve, a cecal carcinoma, or regional ileitis. Prolapse at the stoma in the post-gastrectomy state must not be interpreted as such until a jejunal ulcer or an infiltrating lesion is ruled out.

Summary

Independent motility of the gastrointestinal mucosa and consequent mucosal prolapse at various junctures of changing pressure gradients in the alimentary tract may predispose to clinical disturbances. Most commonly appreciated are rectal mucosal prolapse and benign gastric mucosal prolapse into the duodenum, but ileocecal prolapse, retrograde extrusion of gastric mucosa into the lower esophagus, retrograde prolapse of duodenal mucosa into the stomach, and jejunal mucosal prolapse following surgical anastomoses are less well known. Cases of these are discussed and problems in differential diagnosis are emphasized.

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Discussion

Dr. Maurice Feldman (Baltimore, Md.):—I would like to discuss Dr. Lichstein's paper with special reference to prolapse of gastric mucosa into the duodenum and also comment on other prolapses occurring in the intestinal tract. Detachment of the mucosa may occur anywhere in the gastrointestinal tract. This

phenomenon occurs chiefly where the mucosa is loosely attached to the submucosa and where the mucosa is normally redundant, that is especially in the stomach and rectum. Any long standing hyperperistaltic activity tends to propel the mucosa downward. The roentgenologic incidence of prolapse of the gastric mucosa occurs in about 14 per cent of gastrointestinal cases. The autopsy incidence has not been established. In 1,500 autopsies that we have done, not a single instance was noted, but I might add that this condition has not been sought for and therefore this might account for the lack of autopsy cases. Recently, however, our pathologist has been on the lookout for this condition and found one typical case.

It is of interest to point out in a recent study of 742 cases we found 101 were surgically explored. This incidence of surgical cases represents only the more severe types of cases. It must be emphasized that prolapse of the gastric mucosa is more frequently an incidental finding associated with other conditions. In 48 per cent it is associated with gastritis. Peptic ulcer is likewise noted in an extremely high percentage of cases. The condition is observed in middle-aged and older age groups, especially between the fourth and sixth decades with males predominating.

Although prolapse of the gastric mucosa produces no characteristic clinical pattern, it nevertheless may produce distinct evidence of a pyloroduodenal syndrome. Clinically the condition produces a symptomatology characteristic of a ball and valve syndrome, such as, epigastric distress, pain, nausea, vomiting and bleeding. In the reported surgical cases, pain, discomfort and indigestion occurred in about 65 per cent, gas and fullness in 40 per cent, hematemesis, tarry stools or melena in 40 per cent, nausea and vomiting in 40 per cent and weakness and loss of weight in 40 per cent. Since these represent mostly the surgical cases, this high an incidence of symptomatology does not prevail in the less severe cases. In our clinical study we have found similar symptoms but of a lesser degree, however, the ratio of symptomatology with the reported surgical cases was much lower.

One of the chief features of this condition is a variable degree of prolapse. Although it might be stated that symptoms are more likely to occur in the severe cases, the less severe or moderate prolapses, in many instances also produce symptoms.

Reference has been made to the gastroscopic demonstration of the prolapse. Visualization of the herniated mucosa into the duodenum cannot actually be seen. The marked redundancy of the mucosa, however, directed toward the pyloric outlet is often demonstrable.

Several years ago I suggested that anticholinergic drugs may be used to relieve this condition. Reports of such medical relief have been recorded. The condition is essentially a medical problem which rarely requires surgical intervention. Only in severe cases with intractable symptoms, pyloric obstruction, repeated hemorrhage and obstinate vomiting is surgery indicated.

Of particular interest is the type of retrograde prolapse of the gastric mucosa into the lumen of the lower esophagus. I have reported two such cases. A prolapse of gastric mucosa or jejunal mucosa may occasionally occur following gastrectomy. Often, however, there is an intussusception of the jejunum through the stoma into the stomach. In the case of retrograde prolapse of the duodenal mucosa reported by Dr. Lichstein this is unusually rare since duodenal mucosa is closely adherent to the submucosa. A prolapse resulting from its detachment is not likely to occur. I have never seen such a case.

Prolapse of the ileal mucosa into the cecum is likewise rare. More often the condition is one of lipomatosis infiltration in the region of the ileocecal valve which produces a filling defect simulating a prolapse of the mucosa. Another more common simulating condition occurs in intussusception of the ileum into the cecum.

It is a privilege to have had the opportunity to discuss Dr. Lichstein's paper. I wish to congratulate him for bringing this controversial subject before you, and on his informative and provocative material relating to mucosal prolapse of the gastrointestinal tract.

Dr. Lichstein (*Los Angeles, Calif.*):—May I answer one of the previous questions by Dr. Davis of Van Nuys, California with reference to the simultaneous use of two anticholinergic drugs in the same patient? We have had a good deal of experience in the past two years with the evaluation of Pro-banthine clinically in peptic ulcer and have studied its effect in a preliminary fashion on gastric secretion with regard to its effect on pH, volume and clinical units of acidity and on motility. We know of no report on the use of two such drugs at the same time. As a matter of fact, the individual drugs in this category appear to have become so potent that we are becoming very careful with the use of a single drug let alone a combination of two anticholinergics.

CLINICAL X-RAY STAFF CONFERENCES ON THE COLON*

III. The Importance of Barium Enema in Anorectal Cases

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and
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Grand Rapids, Mich.

In any field of medicine the key to successful treatment is accurate diagnosis. Diseases of the anus and rectum are so situated that they can be inspected, palpated and biopsied. We therefore expect and achieve a very high accuracy of diagnosis in that region. This is indeed commendable and a source of great satisfaction.

There is, however, a joker in this situation. These same anorectal diseases which we diagnose with such a high degree of accuracy may, by producing identical symptoms and signs, mask an important lesion higher in the colon above the reach of direct study. Thus the bleeding, secondary anemia and alteration of bowel habit produced by an easily seen anal ulcer may keep us from realizing that bleeding, secondary anemia and alteration of bowel habit is also occurring as the result of a carcinoma of the descending colon. It is unfortunate that the early evidences of colon malignancy are so often attributable to an obvious and correctly diagnosed lower lesion. Our routine management of anorectal disease must invariably include precautions to avoid this pitfall.

This foregoing concept is not new. It is too often ignored but it should be an invariable part of the philosophy of management of anorectal patients. It means that x-ray investigation of the proximal colon must be done whenever signs of colon disease are present—even though they may be explained by an existing lower lesion.

The next step in developing this train of thought is not as obvious. It consists of recognizing the possibility of completely silent neoplasm of the colon in patients complaining of real or fancied distress referable to the anus and rectum. Examination of these people is completely different from a survey of the general population. These patients are self-screened by their own anxieties and their compulsion to seek out an expert opinion. Even though they do not present overt signs and symptoms which would lead us to suspect neoplasm the very fact that they have sought special care implies an awareness of some colon disability

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From the Ferguson-Droste-Ferguson Hospital, Grand Rapids, Mich.

which may be a first and unrecognizable intimation of serious disorder. When we are consulted by patients in the cancer age group we are morally obligated to be utterly thorough in our examination. This means that our careful examination of the distal 15 per cent of the colon must be supplemented by x-ray investigation of the upper 85 per cent of the colon.

The two cases of this section dramatically illustrate the worthwhile harvest of such thoroughness.

Case 1:—A 76-year old woman consulted us in March of 1953 for treatment of hemorrhoids. Some protrusion and soreness were present. *There had not been*

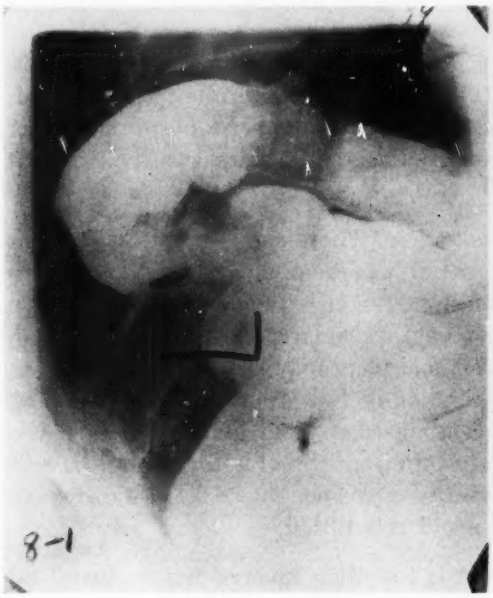

Fig. 1

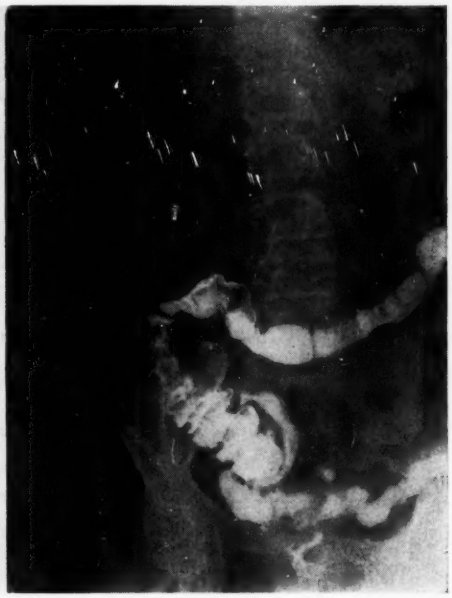

Fig. 2

Fig. 1—Case 1. Spot film of the ascending colon, showing unexpected annular filling defect.
Fig. 2—Case 1. Postevacuation film.

any bleeding. There was no history of tarry stools, no significant change of bowel habit, and no weight loss.

Abdominal examination was negative. Anorectal examination revealed small external hemorrhoidal tabs with large protruding internal hemorrhoids. Proctosigmoidoscopy showed a normal mucosa and lumen to 26 cm. with no evidence of abnormal bowel content. It was the examiner's impression that the patient had external and internal hemorrhoids with severe internal hemorrhoidal protrusion. Hemorrhoidectomy was indicated. In accordance with our standard procedure in such cases, a barium enema was ordered before operation.

Fluoroscopy easily demonstrated a prominent annular filling defect of the distal portion of the ascending colon. It was recorded by spot film (Fig. 1) and

nicely illustrated by postevacuation film (Fig. 2). The filling defect was 4 cm. long. The channel through it was irregular. The rounded bulging ends of the lesion were like the face of a doughnut. The double contrast film (Fig. 3) shows the textbook "applecore" appearance of annular carcinoma.

These x-ray findings startled both the surgeon and the radiologist and forced a drastic revision of the plan of treatment. Right colectomy was done. The patient made a satisfactory recovery.

The surgical specimen was a 35 cm. length of ascending colon and a short segment of terminal ileum together with the attached mesentery and mesocolon. Just distal to the cecum the colon was involved in a cauliflower-like friable

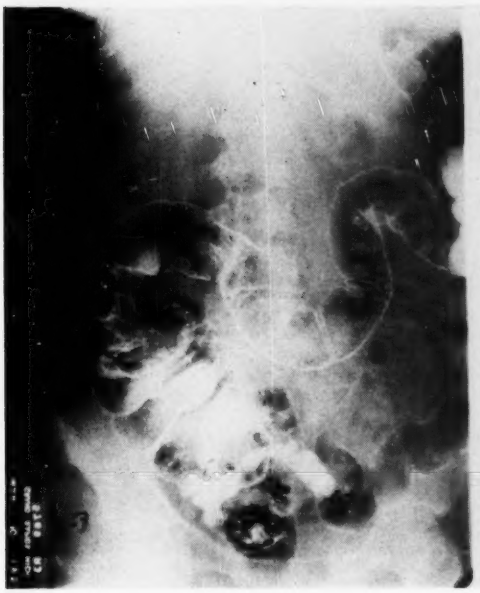

Fig. 3

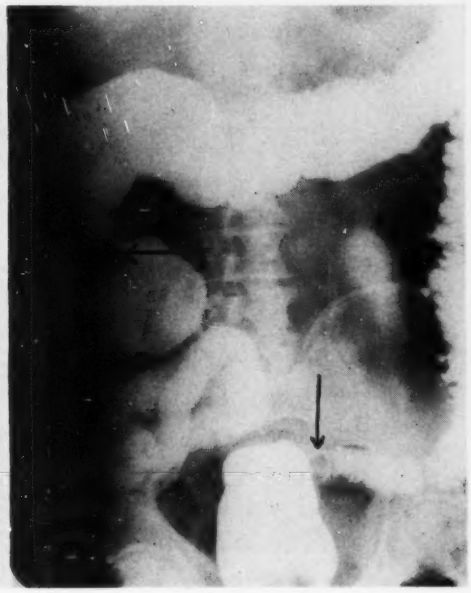

Fig. 4

Fig. 3—Case 1. Double contrast film. Typical "applecore" appearance of annular right colon carcinoma.

Fig. 4—Case 2. First examination. Slight hint of polyp in sigmoid. "Fecal material" in region of ileocecal valve.

tumor mass 8 cm. in diameter, showing multiple ulcerations, and gross extension into the mesocolic fat, with enlargement of numerous lymph nodes. The histologic picture was one of a fairly well differentiated, infiltrating and polypoid adenocarcinoma which had extended to the regional lymph nodes, associated with a good deal of purulent inflammation. Secretory activity was evident in many of the neoplastic extensions, although not a prominent feature of the primary tumor.

Case 2:—A 64-year old white man was seen in March of 1952, complaining of "piles". He had been hospitalized at a general hospital for transurethral resection and the urologist had sent him to us after that operation because of

severe external and internal hemorrhoids. There has been occasional fresh red bleeding with the stool and some protrusion. *There was no history of constipation, diarrhea, tarry stools or weight loss. The appetite was good and the bowel habit entirely normal.*

Regional examination at that time revealed severe external and internal hemorrhoids with protrusion of the internal hemorrhoids. Proctosigmoidoscopic examination was negative to 20 cm. Visualization was not easily achieved, due to the patient's anal discomfort. Barium enema was ordered as a standard procedure in this situation.

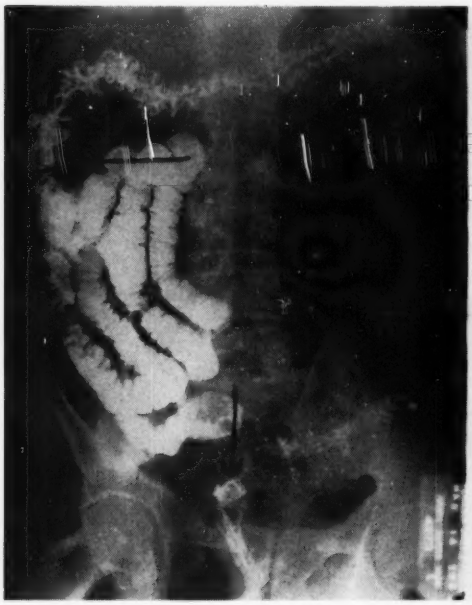

Fig. 5

Fig. 6

Fig. 5—Case 2. Recheck 24 hours later. Postevacuation film demonstrates sigmoid polyp and ascending colon defect.

Fig. 6—Case 2. Double-contrast film provides the clincher in diagnosing ascending colon neoplasm.

Fluoroscopy during the injection of barium was not noteworthy except for the presence of many diverticula of the descending colon. Considerable fecal material was noted at the level of the ileocecal valve. Film studies demonstrated a small oval filling defect in the sigmoid and the fecal material at the ileocecal valve (Fig. 4).

It is, fortunately, our practice to re-examine whenever fecal material is present unless it is in a very finely divided state which can be mixed well with barium during fluoroscopic manipulation and which can be seen to move easily along the colon in the postevacuation film. This patient was therefore rechecked the following day (Fig. 5). The small filling defect of the sigmoid remained

unchanged, indicating the presence of a polyp. The supposed fecal material in the ascending colon was also unchanged in size, shape, and position, and was shown by double contrast film (Fig. 6) to be a fairly large, polypoid neoplasm of the cecum.

In the light of the x-ray findings the patient was thoroughly prepared and proctosigmoidoscopy was repeated, it being possible to reach the sigmoid polyp through the scope, excise it, and fulgerate the base with the electrocautery loop. Right colectomy with end-to-end ileotransverse colostomy was done two days later. The patient's recovery was satisfactory.

Pathologic study showed that the sigmoid polyp measured 10 x 6 mm., and had no visible pedicle. The histology of the lesion was interpreted as showing a pre-invasive stage of adenocarcinoma.

A portion of terminal ileum and right colon were submitted from the same patient. The cecum was involved in a fungating hemorrhagic polyp 7 x 4 cm., possessing a broad pedicle which, on serial section, had a definitely neoplastic appearance, and extended through the muscle coats into the mesocolic attachment. Only two tiny lymph nodes were found in the region of the primary. Two small satellite polyps were present a few cm. distal to the large malignant lesion. The microscopic appearance was that of a papillary adenocarcinoma showing some secretory activity; it had grown through the muscle coats along the lymphatics, without much proliferation in the subserosa. One of the two small lymph nodes contained metastatic tumor.

This patient presented both a silent polyp and a silent right colon malignancy. We are all familiar with silent neoplasms of the colon. Since these lesions are free of subjective and objective findings it would not be possible to discover them all except by submitting the entire population to frequent barium enema. This is not a practical procedure. It is a point of real interest and of importance to determine where to draw the line in deciding which patients shall be required to have x-ray examination of the colon. It is our feeling that a patient of adult years who consults a specialist in diseases of the colon, either a gastroenterologist or a proctologist, should not leave his care still harboring an undiscovered malignant lesion.

From a series of patients typified by the foregoing two cases we can predict that in our practice, in every thousand anorectal patients completely free of any symptom or sign attributable to cancer, we will find six entirely silent neoplasms of the colon. Two of these neoplasms will be carcinomas and four will be polyps, which, of course, are premalignant.

President's Message

Our first regional meeting is now history. The excellent scientific program, the warm hospitality extended to visitors, the unusual attendance from the midwest, all contributed to make it a success. To those who participated in the program, and to the men and women who worked so hard in preparing it, our congratulations and sincere thanks. We hope that this, our first regional meeting, will be followed by many others, and that the same high standard of program will be maintained.

At the meeting of the National Council, further steps were taken to activate the American College of Gastroenterology. The Constitution and By-laws which were approved by the Executive Committee were carefully studied. Numerous amendments were made, and the revision was then approved in its entirety.

Next in order was a meeting of the incorporators of the American College of Gastroenterology at which the Constitution and By-laws were officially adopted and the College, by resolution, was thereupon activated.

The next step will be a meeting of the Fellows of the National Gastroenterological Association to be held in New York City for the purpose of ratifying the actions taken by the National Council.

It was most gratifying to see the enthusiasm and unanimous resolve that was manifest at these meetings.

The American College of Gastroenterology will maintain the highest standards of medical service, and by close correlation with medical schools and recognized gastroenterologists, will attempt to maintain and develop the specialty of gastroenterology, and make it possible for more young men to become well trained in this field,

Our organization will place major emphasis upon research in the field of gastroenterology, both of the laboratory and the clinical type. We shall try to raise the standards of practice in this field, and also attempt to increase the interest of the public as well as of the physicians in the problems of gastroenterology.

Sigurd W. Johnson

EDITORIAL

Infectious Hepatitis

Prevention and dissemination of infectious hepatitis virus is a problem with which physicians have to cope. We know that the virus is present in the feces and the blood. Therefore, it is the duty of the physician to warn the patient and the family that contamination from the infected material must be avoided and that all precautionary measures must be taken to prevent contamination of food, water and milk by feces or flies.

Transmission of the virus may occur through the intestine and/or the blood. Because the virus survives for long periods, homologus serum hepatitis may follow after infusion of 0.01 c.c. of human plasma.

Irradiated plasma is supposed to inactivate one strain of the virus. Unfortunately, this does not guarantee complete immunity as it has been shown that several patients developed jaundice within 70 to 120 days after intravenous infusion of ultraviolet-irradiated plasma. By adding a preservative to the blood, the virus does not survive and the blood is safe for infusion purposes.

Physicians and laboratories should be careful when using syringes and needles to withdraw blood or inject medications intradermally, subcutaneously, intramuscularly or intravenously, that the syringe and needles are sterilized by dry heat at 160° C. for one hour. Hot oil sterilization, or if not feasible, the immersion of the needle in boiling water for 2 to 3 minutes will lessen the danger of transmission of the virus.

Further precautions are the prevention of reflux into the syringe of any body fluid which may be sucked into the needle when giving an intramuscular injection. This may be prevented by pressing the plunger against the bottom of the syringe and maintaining this pressure while withdrawing the needle. We have found this the most reliable protection against any reflux during or after injection.

The use of gamma globulin as a preventive of viral hepatitis has been found efficacious when given early and to confer passive immunity for 6 to 8 months. It is of no value when given later in the incubation period or when used against serum hepatitis. Doses as small as 0.01 c.c. per pound of body weight are effective.

Patients under the care of physicians should be made to understand that the disease is self-limited, lasting from 4 to 8 weeks without residual liver damage in most cases. Relapses may occur with eventual recovery. It is, therefore, essential that these patients remain in bed, as early ambulation, dietary and alcoholic debauches may lead to a fatal outcome. When relapses occur, jaundice need not be present, the liver becomes enlarged, tender and liver function tests show various deviations from normal.

Many patients continue to complain of anorexia, lassitude and fatigue long after the acute condition disappears. These patients are suffering from subacute hepatitis, either in the mild form or, if progressive and it continues for many months, they go downhill, may develop ascites, bleeding and hyperglobulinemia. Operation or autopsy reveals a small nodular liver.

There are two other types of hepatitis—the recurrent and the chronic with cirrhosis. In the recurrent type, relapses occur over many months or years with periods of quiescence, finally resulting in a nodular liver.

In chronic hepatitis and cirrhosis, the patients show abnormal liver function tests and on biopsy, cellular infiltration, fibrosis and nodular regeneration is found. These findings are characteristic of cirrhosis. One of the most reliable tests in the differentiation, besides the biopsy, is the bromsulfalein excretion test, using 5 mg. of the dye per kilogram of body weight and examining the blood 45 minutes after injection of the dye into the vein of one arm and withdrawing the blood from the other arm.

SAMUEL WEISS, M.D.

ABSTRACTS FOR GASTROENTEROLOGISTS

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INTESTINES

NEWER THERAPEUTIC METHODS IN ULCERATIVE COLITIS: A. Staehelin. Schweiz. Med. Wchnschr., 83:883, (Sept. 19), 1953.

Surgical therapy in ulcerative colitis is only indicated in severe complications. In the acute phase, colectomies are performed only for alarming hemorrhage. Individualized therapy is laborous and takes a long time. Therapy is based on bed rest, transfusions, infusions, vitamins, iron preparations, stimulation. In the presence of rectal involvement enemas of Dermatol should be given, while in hypopotassemia, peroral administration of Potassium Citrate is important. Dietary therapy must be individualized. It should not only be low residue but also high in calories and particularly in proteins.

While the enthusiasm concerning sulfonamides has subsided they still have a place in therapy of colitis. Penicillin and streptomycin have not entailed any decisive advance but should be tried in febrile cases. Aureomycin seems to exert a beneficial effect but intermittent therapy is advised. The effects of chloromycetin and terramycin were less favorable. ACTH and cortisone seem to be indicated in only selected cases where danger of perforation does not exist.

The only therapy which hits the cause of the disease is psychotherapy. It has been shown that the colon responds to certain psychic noxae with hypodynamia and constipation or with hyperdynamia and diarrhea. The hyperfunctional responses are associated with hyperemia and intense contractions of the circular and longitudinal musculature. This reaction can be produced by bacteria, increased intestinal contents, and by mental factors such as fear, rejection, guilt, and "conflicts". Patients with colitis show a superficial calmness but have repressed rage and hostility of great urgency. Such individuals respond to psychic traumata with colonic hyperfunction associated with increased susceptibility of the mucosa to injury. The combination of hypermotility, hyperemia, hemorrhages, increased lysozyme excretion, increased mucosal sensitivity, and the large numbers of bacteria in the colon is capable of producing the characteristic ulceration.

REGINALD B. WEILER

SIGNIFICANCE AND TREATMENT OF POLYPS OF THE COLON AND RECTUM: N. W. Swinton and W. A. Doane. New England J. Med., 249:17, (Oct. 22), 1953.

A reveiew of 400 patients treated at the Lahey Clinic between 1945 and 1950 with polyps of the colon and rectum is presented showing that benign mucosal polyps of the rectum and colon occur in both sexes, slightly more often in males than in females, and at all ages; that they are often multiple and occurred in 25 per cent of all surgical specimens removed for cancer of these organs. There was a definite similarity between the location of benign mucosal polyps and carcinoma of the rectum and colon. Also it was seen that all stages between benign mucosal polyps and carcinoma of the colon and rectum could be demonstrated histologically. These benign mucosal polyps must be considered as premalignant lesions and since a high percentage of malignant lesions

of the colon and rectum originate in a pre-existing benign mucosal polyp, such pre-malignant lesions should be removed or destroyed without delay.

The importance of careful sigmoidoscopic examination, even to the point of using this particular instrument as part of routine diagnostic work, was emphasized.

Of the 400 patients reported, the polyps in 230 cases were destroyed by fulguration, 44 were removed by snare excision and fulguration, 34 by surgical excision and 30 by colectomy. Sixty-nine patients required some type of resection and four patients refused treatment.

Pathologically, 38 cases were reported as benign mucosal polyps with early carcinoma, 50 cases of carcinoma of the rectum with benign mucosal polyps and 19 cases of carcinoma of the colon associated with benign mucosal polyps were included.

The authors conclude with a strong plea for the proper examination and removal of polyps if found, stressing that this is the ideal approach to the problem of cancer of the terminal bowel.

WILLIAM E. JONES

DIAGNOSIS AND TREATMENT OF THE IRRITABLE COLON SYNDROME: Edward J. Donovan. Rocky Mountain M. J., 50:952-956, (Dec.), 1953.

Symptoms of colonic dysfunction can arise from functional disturbances alone. The gastrointestinal tract functions on a neuromuscular-glandular basis and so is subject to disturbances from emotional and irritative stimuli. Neuromuscular manifestations include: spasm, atony, constipation, diarrhea, pain, nausea, regurgitation, anorexia, epigastric distress, and pylorospasm. Secretory dysfunction is characterized by: excessive mucus secretion and hyperchlorhydria. The fundamental factor is an imbalance between the neuromuscular relationship. Much unneeded surgery has resulted from lack of such appreciation. The etiology of the irritable colon is either psychogenic or "abuse" of the digestive tract. The symptoms vary from patient to patient and in the same patient but mostly the symptoms are of long duration without effect on the general health. Rest is the key note of therapy with management of psychic factors.

REGINALD B. WEILER

USE OF HYDROGEN PEROXIDE FOR THE ELIMINATION OF GAS FROM THE INTESTINE DURING ROENTGENOGRAPHY OF THE ABDOMINAL VISCERA: A. Govoni, J. F. Brailsford and E. H. Mucklow. Am. J. Roentgenol., pp. 235-238, (Feb.), 1954.

The patient is given an enema at body temperature, the fluid consisting of 10 c.c. of hydrogen peroxide (40 vol.) per liter of water. This is introduced slowly, the patient changing his position from the prone to the left side, to supine, to the right side lying on this side for a short time. It is important that the patient evacuate at the first symptom of abdominal colic, otherwise there will be a defective elimination of the gases. To insure success, special attention should be given to the diet for the two days preceding examination excluding legumes, etc., in order to insure a low residue in the colon. The results as shown in the roentgenograms published seem impressive.

J. R. VAN DYNE

ORAL MECHANISMS IN CONSTIPATION AND DIARRHEA: T. S. Szasz. Internat. J. Psychoanal. 32:196-203, 1951.

A study was made of the psychodynamic formulations of anorexia-bulemia associated with constipation. Activation of oral-incorporative tendencies (the drives associated with the second six months of life in respect to the maternal breast) is associated with constipation. Where there is anticipation of satisfaction, actual satisfaction or inhibition of these drives colonic activity increased with relief of constipation or onset of diarrhea. Similar findings were present in ulcerative colitis.

REGINALD B. WEILER

DIARRHEA IN INFANTS AND CHILDREN: Kenneth P. Crawford. J. Kentucky M. A., 51:425, (Oct.), 1953.

Diarrhea may be caused by external, enteric, or parenteral factors. Predisposition is related to age, weather, bodily resistance, hygiene, and food. Bacteria responsible include: dysentery bacilli; Salmonella group, streptococci, staphylococci; "Friedländer's bacillus", Proteus vulgaris, Protens morganii, Pseudomonas aeruginosa, Endameba histolytica, and certain strains of E. Coli. Also etiologically significant at times are: starvation, celiac disorders, laxatives, nervous tension, and adrenocortical insufficiency. Several types of diarrheal symptoms exist. Dehydration is a serious complication. The treatment includes: Starvation from 12 to 36 hours, during which sterile water, 5 per cent glucose water or 5 per cent "Arobon" water is given. Then skimmed milk sometimes with 5 per cent "Arobon" is started. Kaolinpectin mixtures, bismuth preparations, "Appella powder", pectin, and tomato-pectin are available. Resion given every hour in tablespoonful doses for 4 hours, then every 2 to 4 hours is valuable. Dehydration must be corrected and acidosis and shock combatted. An initial infusion of psysiological salt solution 10 c.c. per pound of weight establishes renal flow. If acidosis threatens supplemental equal quantity of ⅙ molar sodium lactate is injected. After renal flow is reestablished plasma or blood equal to 10 c.c. per pound is given. Glucose solution should be added so as to make 100 c.c. of liquid available per pound in 24 hours. Hypopotassemia should be combatted by giving the salt in the infusions. If needed, calcium preparations may also be included. Specific drug therapy should be started as soon as determination of the most available one is made. Penicillin serves to combat secondary infection, streptomycin may be given to the more severe cases, and as soon as renal function is reestablished the sulfonamides are indicated. It is emphasized that—(1) the condition is to be taken seriously; (2) the patient should be examined and (3) watch the case carefully.

REGINALD B. WEILER

PATHOLOGY AND LABORATORY RESEARCH

HUMORAL EFFECTS OF STENOSIS OF THE PYLORUS IN ADULTS: A. Monsaingeon, P. Tanret and J. J. Bernier. Arch. mal. app. dig. 42:3, (March), 1953.

This report has a dual purpose: the clarification of the principal data known on this question of digestive physiopathology and the study of certain problems so far not satisfactorily solved.

Its interest exceeds that of pure stenoses since, if these have become rare, the humoral effects of gastric suction and acute dilatation of the stomach raise similar problems.

The electrolytic study made was concerned with an extreme type of experimental stenosis in which spoliation was particularly brutal and differentiated—notably histaminic hypersecretion on a completely stenosed stomach. The report does not give details of the experiments carried out, but gives the conclusions drawn. Some well-known ones are concerned with hypochloremia, alkalosis; others take into consideration more recent data, notably the changes in sodium whose plasmatic variations do not correspond to losses observed in the urine and the gastric fluid and must express changes in the distribution of the extracellular sector towards the intracellular sector. The changes in potassium are also described as are the changes in the water of the intra sector towards plasma. All these mutations of electrolytes are liable to great variations depending on the composition of the gastric juice.

The water loss may be compensated for in any part by a certain absorption of water by the stenosed stomach. The main consequence is that a well maintained diuresis does not allow the hypothesis of a certain degree of dehydration to be ruled out. The maintenance of diuresis is in itself the cause of the electrolytic loss and notably of a loss of Vitamin K which may produce a real syndrome of hypochloremia with hypokalemia and alkalosis.

In all these facts, the problem which presents itself is that of the origin of the water lost. Certain arguments enable one to consider the immediate importance of the participation of the intracellular liquids which, in the most acute forms would play a most important part.

Renal effects of stenoses of the pylorus raise a vast and badly elucidated problem in which occur excessive nitrogenous catabol-

ism with probable intracellular dehydration, renal effects of the loss of extracellular liquids and of alkalosis as such.

The effects of treatment are easier to understand if one bears in mind the composition of the liquids most commonly employed. The ionogram of these liquids should be studied and compared with that of plasma. The hazards of treatment are of two varieties:

Either to ensure excessive diuresis by a predominantly glucose administration and without giving any electrolytes, or to surcharge the organism with electrolytes, notably by hypertonic solutions without the necessary supply of water.

The addition of potassium to the substitute treatment has constituted a progress whose origin (in studies of metabolism) and whose significance (at the level of the intracellular liquids) it is not without interest to reveal.

FRANZ J. LUST

RESPONSE OF THE INTRAGASTRIC TEMPERATURE TO VARIOUS DRUGS: Hisayuki Masuda, Mitsuo Ohara and Shigeaki Katsura. Tohoku J. Exper. Med., 57:129-137, (Feb.), 1953.

These are the fifth and sixth reports of the authors on their studies of the temperature of the gastrointestinal tract. The response of the intragastric temperature of healthy men to subcutaneous injections of histamine, adrenalin, pilocarpine and atropine was studied simultaneously with those of the axillary temperature, pulse, blood pressure and gastric juice. It was found: (1) The intragastric temperature drops by the four drugs. (2) The drop by histamine is transient, in contrast to that of adrenalin and pilocarpine. The drop by atropine is preceded by a slight rise. (3) The maximum drop is large by histamine and pilocarpine, small by adrenalin and atropine. (4) The onset of the drop is more rapid by histamine, slowest by atropine. (5) The change in the axillary temperature is generally parallel with that inside the stomach. (6) Change in the pulse rate is in intimate relation with that in the intragastric temperature. Blood flow is one of the most important factors in the change in the intragastric temperature. (7) By histamine and pilocarpine, which strongly stimulate the gastric secretion, the intragastric temperature is intensely lowered.

The response to subcutaneous injection of benzylimidazoline, to intravenous injection of the same drug and tetraethylammonium bromide was studied. The intragastric temperature drops by the two latter drugs. The drop by histamine is the greatest and both the onset and the recovery is the most rapid. The change in intragastric temperature is not related to that of the gastric free acidity.

FRANZ J. LUST

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BROMIDE
(OXYPHENONIUM BROMIDE CIBA)

for demonstrable benefit in peptic ulcer

THE PATIENT FEELS
ulcer pain is rapidly controlled (often within 24-36 hours); relief lasts with continuing treatment.

YOU OBSERVE
almost uniformly good response and progress toward healing; few and generally mild by-effects.

THE LITERATURE REPORTS
50 out of 52 responding to Antrenyl; [1] complete relief in *all* of 24 cases; [2] 33 of 39 patients healed or improved. [3] Antrenyl is a valuable adjunct to dietary and other ulcer measures. Tablets, 5 mg., Syrup, 5 mg. per 4 ml.

1. Rowen, B.R., Bachrach, W.H., Halsted, J.A., and Schapiro, H.: Gastroenterology 24:86, 1953.
2. Rogers, M.P., and Gray, C.L.: Am. J. Digest. Dis. 19:180, 1952.
3. Schaub, K.: Praxis 41:1073, 1952.

Ciba *Summit, N. J.*

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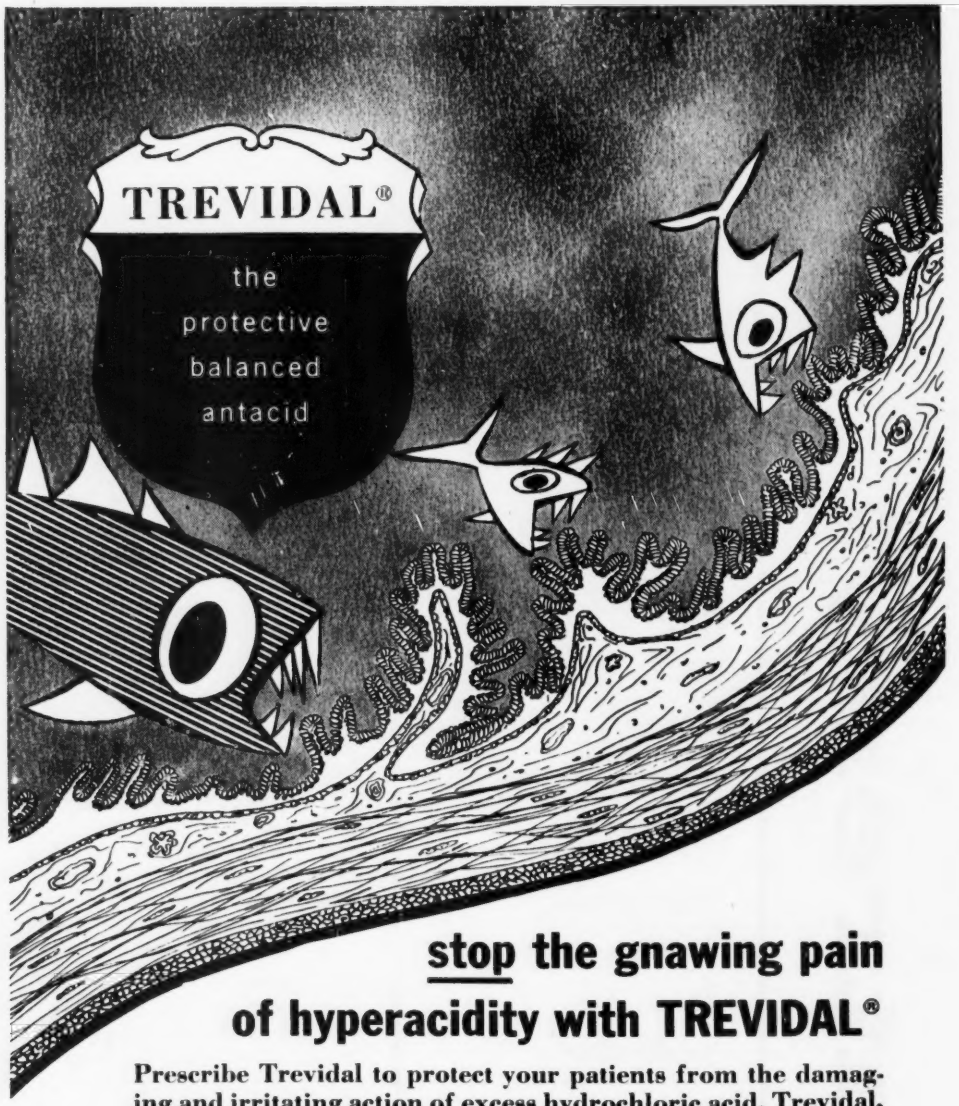

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brand of tetracycline

whenever you take a temperature

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for an *afebrile in *hours* response

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- unexcelled tolerance
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250 mg., 100 mg., 50 mg.

TETRACYN ORAL SUSPENSION (*amphoteric*) (*chocolate flavored*) 250 mg. per 5 cc. teaspoonful; in 1 fl. oz. bottles containing 1.5 Gm.

TETRACYN INTRAVENOUS
Vials of 250 mg. and 500 mg.

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½ oz. and 1 oz. tubes. Each Gm. contains 30 mg. crystalline tetracycline hydrochloride.

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Under his jacket

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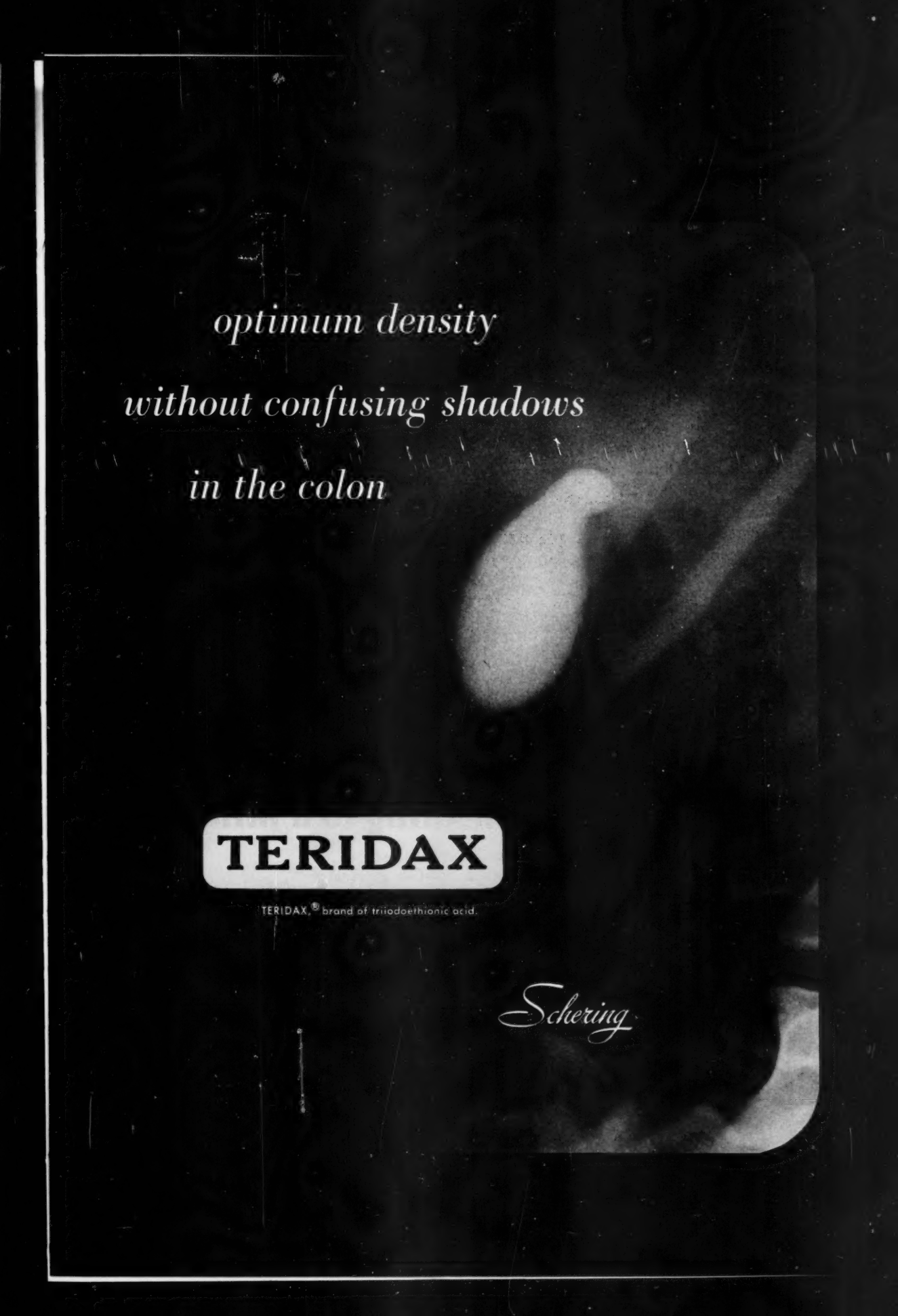
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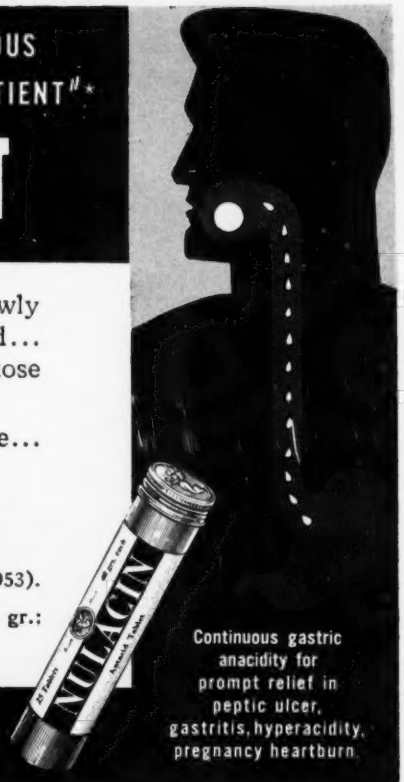
A pleasant-tasting tablet...to be dissolved slowly in the mouth...not to be chewed or swallowed... made from milk combined with dextrins and maltose and four balanced nonsystemic antacids...**

Promptly stops ulcer pain...holds it in abeyance... hastens ulcer healing.

In tubes of 25 at all pharmacies. Physicians are invited to send for reprints and clinical test samples.

*Steigmann, F., and Goldberg, E., J. Lab. & Clin. Med. *42*:955 (1953).

**Mg trisilicate, 3.5 gr.; Ca carbonate, 2.0 gr.; Mg oxide, 2.0 gr.: Mg carbonate, 0.5 gr.



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Disposable Unit

Polyethylene "squeeze bottle" permits easy one-hand administration... rectal tube kept sanitary by sealed cellophane envelope... distinctive rubber diaphragm prevents leakage while controlling flow. Because of these unique features, FLEET ENEMA Disposable Unit is preferred for hospital, clinic and office use.

Each single use unit of 4½ fl. ozs., contains in each 100 cc., 16 Gm. sodium biphosphate and 6 Gm. sodium phosphate,... an enema solution of Phospho-Soda (Fleet), gentle, prompt, thorough—and as effective as the average enema of one or two pints.

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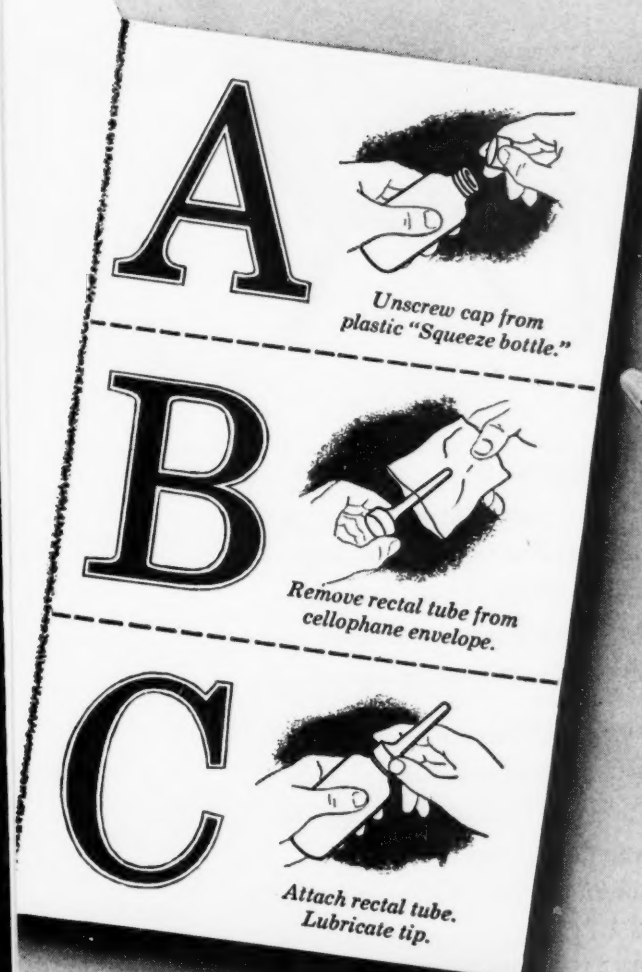

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TRICREAMALATE®

for the patient

with an

"eccentric"

ulcer

Roentgenographically, their peptic ulcers may appear about the same. But the "eccentric" ulcer patients bleed easily, have frequent flare-ups, and suffer from persistent pain. Tricreamalate in such a case often gives relief and even helps to avoid surgery.

Tricreamalate (*reactive* aluminum hydroxide *plus* hydrated magnesium trisilicate) stops pain fast — prevents recurrences — helps to control bleeding — is nonconstipating — prolongs buffering action. Liquid and tablets for PEPTIC ULCER and GASTRIC HYPERACIDITY.

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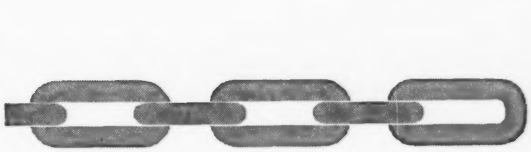
"where oozing from a vascular bed is anticipated"*

ADRENOSEM stops capillary bleeding and oozing. Adrenosem acts directly on the capillary walls to increase resistance and decrease permeability.

There are no reported toxic effects or contraindications attributable to Adrenosem. Adrenosem does not affect blood components or induce embolus formation. It has no sympathomimetic or vasoconstrictive action. Adrenosem is compatible with vitamin K, heparin, and commonly used anesthetics. (It is suggested, however, that antihistamines be withheld for 48 hours prior to and during Adrenosem therapy since antihistamines tend to inactivate Adrenosem.)

*Sherber, D. A.: The Control of Bleeding. Am. J. Surg. *86*:331 (Sept.) 1953.



adrenosem

the missing link in the control of bleeding

The therapeutic regimen for Adrenosem is *simple* and *safe:*

- *preoperatively* to control oozing during surgery and provide clearer operative field: one to two ampuls (5 to 10 mg.) every two hours prior to surgery for two doses.
- *postoperatively* to prevent hemorrhage and check oozing: one to two ampuls (5 to 10 mg.) every two hours until there is no indication of undue bleeding. To maintain control, one ampul may be administered every three hours or 1 to 5 mg. orally t. i. d.
- to control *active bleeding:* One ampul (5 mg. every two hours until bleeding is controlled; frequency of dose may then be diminished.
- to control *severe bleeding:* one ampul (5 mg.) every hour for three doses; then every three hours until bleeding is controlled.
- to control *mild, low-grade bleeding:* 1 ampul (5 mg.) every three or four hours until bleeding is controlled; then 1 to 5 mg. orally four to five times daily until bleeding ceases.
- *maintenance dosage* to prevent bleeding in conditions where small vessel integrity may be impaired: 1 to 5 mg. orally t. i.d.; if bleeding ensues, dosage may be increased 1 to 5 mg. orally every three or four hours; if bleeding persists, oral dosage should be supplemented with 1 ampul (5 mg.) daily.
- *pediatric dosage:* up to four years of age – 1 mg. intramuscularly or orally with same frequency as for adults, until bleeding is controlled. From four to twelve years of age – ½ the adult dosage as indicated.

Available as Ampuls: 5 mg., 1 cc. (package of 5).
Tablets: 1 mg. S. C. Orange, bottles of 50.
Tablets: 2.5 mg. S. C. Yellow, bottles of 50.

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Aluminum Hydroxide Gel with Magnesium Hydroxide

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